UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: 05-MAR-2018

Subject: **Clethodim (121011);** Petition for the Establishment of Uses and Permanent Tolerances for Tree Nuts, Group 14-12, Okra, Crop Group Conversions and Expansion of Tolerances to cover Subgroup Tolerances and Review of 6(a)2 Data. **Summary of Analytical Chemistry and Residue Data.**

PC Code: 121011	**DP Barcodes:** D436731 (petition), D390071 (6(a)2 data)
Decision No.: 521261, 390071	**Registration No.:** 59639-3, 59639-132
Petition No.: 6E8510	**Regulatory Action:** Section 3 registration & 6(a)2 data
Risk Assessment Type: not applicable	**Case No.:** 7226
TXR No.: not applicable	**CAS No.:** 99129-21-2
MRID No: see below	**40 CFR:** §180.458

From: William D. Wassell, Chemist
Health Effects Division/Risk Assessment Branch 3 (HED/RAB3, 7509P)

THROUGH: Tom Moriarty, Branch Chief
RAB 3/HED (7509P)

To: S. Jackson, RM 05
and
N. Anderson/Ricardo Jones RM51
Registration Division (RD; 7505P)

Summary of Submitted/Reviewed Residue Chemistry Studies	
OCSPP Guideline	Reference
860.1300	49527101. Dohn, D. *et al.* (2009). The Metabolism of (carbon 14) Clethodim (2 Radiolabels) in Carrot (*Daucus carota*). Project Number: 1808W, 1808W/1. Unpublished study submitted by Valent U.S.A. Corporation, Walnut Creek, CA. 304 p.
860.1300	49527102. Dohn, D. *et al.* (2010). The Metabolism of (carbon 14) Clethodim (2 Radiolabels) in Spinach (*Spinacea oleracea*). Project Number: 1809W, 1809/1. Unpublished study submitted by Valent U.S.A. Corporation, Walnut Creek, CA. 257 p.
860.1500	49958401. Leonard, R. (2015). Clethodim: Magnitude of Residue on Okra. Project Number: 10383. Unpublished study submitted by The Interregional Research Project No. 4. Princeton, NJ. 293 p.
860.1500	49958402. Lennon, G. (2016). Clethodim: Magnitude of Residue on Almond. Project Number: 11093, 11093/13/YAR03. Unpublished study submitted by The Interregional Research Project No. 4. Princeton, NJ. 284 p.
860.1500	49958403. Lennon, G. (2016). Clethodim: Magnitude of Residue on Pecan. Project Number: 11094, 11094/13/YAR04. Unpublished study submitted by The Interregional Research Project No. 4. Princeton, NJ. 241 p.

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1.0 Executive Summary

Background: Clethodim [2-[1-[[[(2*E*)-3-chloro-2-propenyl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one] is a selective postemergence cyclohexenone herbicide registered for use on a variety of field and vegetable crops for the control of annual and perennial grasses; it does not control sedges or broadleaf weeds. Permanent tolerances have been established under 40 CFR §180.458(a)(1) for the combined residues of the herbicide clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexen-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexen-3-one moieties and their sulfoxides and sulphones in/on various plant commodities at levels ranging from 0.20 ppm (many commodities) to 20 ppm (clover, hay). Clethodim is currently registered to Valent U.S.A. Corporation as an emulsifiable concentrate (EC) formulation containing either 2.0 lb ai per gallon (EPA Reg. No. 59639-3) or 0.97 lb ai per gallon (EPA Reg. No. 59639-132).

Additionally, Valent has submitted 2 studies as 6(a)2 data. The submitted studies are plant metabolism studies.

The Interregional Research Project No. 4 (IR-4) has proposed uses and tolerances for residues of clethodim, including its metabolites and degrades, in or on the following commodities:

Raw Agricultural Commodities/Crop Group	**Proposed Tolerance (ppm)**
Nuts, Tree, Group 14-12	0.2
Almond, Hulls	0.2
Okra	1.5
Vegetable, Fruiting, Group 8-10 except okra	1.0[1]
Stalk and Stem Vegetable, Subgroup 22A	1.7[2]
Vegetable, *Brassica*, Head and Stem, Group 5-16	3.0[3]
Brassica, Leafy Greens, Subgroup 4-16B	3.0[4]
Leaf Petiole Vegetable, Subgroup 22B	0.60[5]
Leafy Greens, Subgroup 4-16A	2.0[6]
Onion, green, Subgroup 3-07B	2.0[7]

[1] Request to revise tolerance from Vegetable, Fruiting, Group 8-10 to Vegetable, Fruiting, Group 8-10, except okra based on currently submitted data for clethodim in/on okra.
[2] Based on current tolerance for clethodim at 1.7 ppm in/on asparagus.
[3] Request for conversion of the currently established tolerance for clethodim at 3.0 ppm in/on *Brassica*, Head and Stem, Subgroup 5A to Vegetable, *Brassica*, Head and Stem, Group 5-16.
[4] Request for conversion of the currently established tolerance for clethodim at 3.0 ppm in/on *Brassica*, Leafy Greens, Subgroup 5B to *Brassica*, Leafy Greens, Subgroup 4-16A.
[5] Request for conversion of the currently established tolerance for clethodim at 0.60 ppm on Leaf Petiole, Subgroup 4B to Leaf Petiole Vegetable subgroup 22B.
[6] Request for conversion of the currently established tolerance for clethodim at 2.0 ppm on Leafy Greens, Subgroup 4A to Leafy Greens, Subgroup 4-16A.
[7] Request for conversion of the currently established tolerance for clethodim at 0.60 ppm on Leaf Petiole, Subgroup 4B to Leaf Petiole Vegetable subgroup 22B.

IR-4 further proposes, upon establishment of the requested tolerances, to remove established tolerances for residues of the herbicide clethodim, including its metabolites and degrades, in or on the commodities listed in the following table.

Raw Agricultural Commodities/Crop Group	**Propose Tolerance (ppm)**
Asparagus	1.7
Brassica, Head and Stem, Subgroup 5A	3.0

Brassica, Leafy Greens, Subgroup 5B	3.0
Leafy Petioles, Subgroup 4B	0.60
Leafy Greens, Subgroup 5B	2.0
Onion, green	2.0
Turnip Greens	3.0
Vegetable, Fruiting, Group 8-10	1.0

Proposed Use: IR-4 has submitted proposed use directions for V-10137 1 EC Herbicide (also known as Select Max Herbicide) (EPA Reg. No. 56939-132; 0.97 lb ai per gallon; formulated as a EC) and Select 2 EC Herbicide (EPA Reg. No. 56939-3; 2.0 lb ai per gallon; formulated as a EC) which include instructions for applications to tree nuts and okra. For tree nuts, up to 4 applications may be made at 0.09 to 0.125 lb ai/A for control of annual and perennial grasses. A retreatment interval (RTI) of 14 days between application and a pre-harvest interval (PHI) of 14 days are specified. A maximum of 0.5 lb ai/A may be applied per crop year. The use directions for V-10137 1 EC Herbicide specify that a nonionic surfactant (NIS) should be included in the spray. The directions for Select 2 EC Herbicide specify that a crop oil concentrate (COC) should be included in the spray.

For okra, up to 4 applications may be made at 0.09 to 0.125 lb ai/A for control of annual and perennial grasses. A RTI of 14 days between applications and a PHI of 3 days are specified. A maximum of 0.5 lb ai/A may be applied per crop year. The use directions for V-10137 1 EC Herbicide specify that a NIS should be included in the spray. The directions for Select 2 EC Herbicide specify that a COC should be included in the spray.

The proposed application scenarios are supported by the submitted residue chemistry data.

Nature of the Residue - Primary Crops/Rotational Crops/Livestock: The nature of the residue in plants is adequately understood based on the available metabolism studies on carrot, soybean, cotton, and the foliage of these crops. The metabolism studies on these crops combined with the confined rotational crop data from carrot, wheat, and lettuce provide adequate information to define the metabolic profile across numerous crops.

The submitted metabolism studies (6(a)2 data) do not alter our previous conclusions concerning the residues of concern.

Based on the available data, HED determined that the residues of concern in primary crops are clethodim and its metabolites containing the 2-cyclohexen-1-one moiety; however, in order to harmonize with Codex, HED determined that the tolerance should be expressed as clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.

The nature of the residue in the livestock is adequately understood based on acceptable ruminant (goat) and poultry (laying hen) metabolism studies. HED has determined that the residues of concern in meat, milk, poultry, and eggs are clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.

Based on these data, HED concluded that the residues of concern, for tolerance enforcement and risk assessment, are as defined in Table 4.0.1.

Magnitude of the Residue - Proposed Crops: The number and geographical representation of the submitted okra, almond, and pecan field trial data are adequate. All samples were analyzed using adequately validated methods and sufficient storage stability data are available. Based on these field trial data, HED concludes that the tolerances listed in Table 2.2.2.1. for residues of clethodim, including its metabolites and degradates, are appropriate.

Magnitude of the Residue - Rotational Crops: Data concerning the magnitude of residue in rotational crops are not required. The magnitude and nature of the residue in rotational crops is adequately understood based on confined rotational crop studies with rotated carrots, lettuce, and wheat. The results indicate that there is no need for field rotational crop trials and that a 1-month plantback interval will be appropriate for all crops not included on the label. The submitted labels include the following restriction: do not plant rotational crops until 30 days after application of Select 2 EC Herbicide and V-10137 1 EC Herbicide.

Magnitude of the Residue – Livestock: Livestock commodity tolerances for residues of clethodim are currently established. The only feed commodity associated with the subject petition are almond hulls. Almond hulls are considered a roughage supplement to the livestock diet. Clethodim is registered for use on many roughage supplements such as alfalfa, clover, field corn (forage/silage and stover), and peanut (hay). The addition of almond hulls to the diet does not alter our previous conclusions concerning livestock commodity tolerances.

2.0 Recommendations

Provided the petitioner submits a revised Section B/proposed use and Section F/proposed tolerances, HED concludes that the residue chemistry database supports the establishment of the permanent tolerances listed in Section 2.2.2. A human health risk assessment is forthcoming.

2.1 Data Deficiencies/Data Needs

- Revised Section B/proposed use.
- Revised Section F/proposed tolerances.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

References:
Memo, 04/13/2016, M. Negussie, D431225

Adequate analytical methods are available for enforcing clethodim tolerances in/on the proposed/registered plant commodities. Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using the gas chromatography/mass spectroscopy (GC/MS) Method YARL-0602D, adapted from Method RM-26B-3 entitled, "The Determination of Clethodim Residues in Crops, Chicken and Beef Tissues, Milk and Eggs" (revision dated January 20, 1994). The method converts residues of clethodim and metabolites to clethodim sulfoxide (CSO) and clethodim 5 hydroxy sulfoxide (5-OH CSO2) which are determined as their dimethyl esters (DME and DME-OH, respectively). Method RM-26B-3 is the enforcement method for tolerances for clethodim including its metabolites and degradates.

2.2.2 Recommended Tolerances

HED has reviewed the available residue data and has determined the appropriate tolerance levels for residues of clethodim (Table 2.2.2.1). The tolerance expression is as follows:

(a) *General.* Tolerances are established for residues of the herbicide clethodim, including its metabolites and degradates, in or on the commodities in the table in this paragraph. Compliance with the tolerance levels specified in this paragraph is to be determined by measuring only the sum of clethodim, 2-[(1*E*)-1-[[[(2*E*)-3-chloro-2-propenyl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one, and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, calculated as the stoichiometric equivalent of clethodim, in or on the commodity.

HED concludes the tolerance expression is in compliance with current guidance and does not need to be revised.

Table 2.2.2.1. Tolerance Summary for Clethodim.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Nuts, Tree, Group 14-12	0.2	0.20	
Almond, Hulls	0.2	0.20	
Okra	1.5	1.5	
Vegetable, Fruiting, Group 8-10 except okra	1.0		
Stalk and Stem Vegetable, Subgroup 22A	1.7	1.7	
Vegetable, *Brassica*, Head and Stem, Group 5-16	3.0		
Brassica, Leafy Greens, Subgroup 4-16B	3.0		
Leaf Petiole Vegetable, Subgroup 22B	0.60		
Leafy Greens, Subgroup 4-16A	2.0		
Onion, green, Subgroup 3-07B	2.0		

Upon establishment of the requested tolerances, remove established tolerances for residues of the herbicide clethodim, including its metabolites and degrades, in or on the commodities listed in the following table.

Raw Agricultural Commodities/Crop Group	**Established Tolerance (ppm)**
Asparagus	1.7
Brassica, Head and Stem, Subgroup 5A	3.0
Brassica, Leafy Greens, Subgroup 5B	3.0
Leafy Petioles, Subgroup 4B	0.60
Leafy Greens, Subgroup 5B	2.0
Onion, green	2.0
Turnip Greens	3.0
Vegetable, Fruiting, Group 8-10	1.0

2.2.3 Revisions to Petitioned-For Tolerances

The proposed tolerance levels were not revised; however, the number of significant figures on the tolerance level for residues in/on tree nuts, group 14-12, and almond hulls were modified. A revised Section F/proposed tolerances is required.

2.2.4 International Harmonization

There are no Codex, Canadian or Mexican maximum residue limits (MRLs) for clethodim and its metabolites in/on the crops of interest. Thus, harmonization of tolerances/MRLs are not an issue for this petition.

2.3 Label Recommendations

A revised Section B/proposed use is required. The use directions for fruiting vegetables, except okra and tomato, crop Group 8-10 on the Select 2 EC label and V-10137 1 EC need to be modified to indicate the use directions apply to "fruiting vegetables, except okra, group 8-10."

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of clethodim and metabolites of interest are presented in Table 3.1.1.

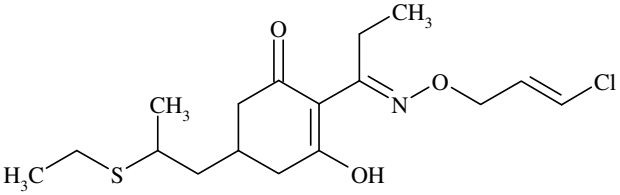
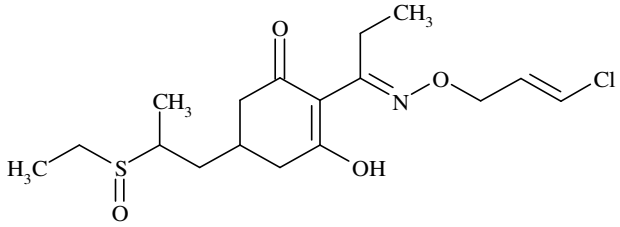
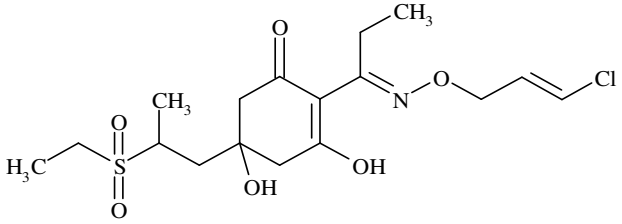
Table 3.1.1. Nomenclature for Clethodim and Metabolites of Interest.	
Common name	Clethodim
CAS Nomenclature	2-[1-[[[(2*E*)-3-chloro-2-propenyl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one
IUPAC Nomenclature	(5*RS*)-2-{(1*EZ*)-1-[(2*E*)-3-chloroallyloxyimino]propyl}-5-[(2*RS*)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one
CAS registry number	99129-21-2
Molecular weight	359.92 g/mol
Company experimental name	Not applicable
	
Metabolite	Clethodim sulfoxide (CSO)
Identity	[(*E,E*)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfinyl) propyl]-3-hydroxy-2-cyclohexen-1-one]
Molecular weight	375.92 g/mol
	
Metabolite	5-OH Clethodim sulfone (5-OH CSO2)
Identity	[(*E,E*)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfonyl)

Table 3.1.1. Nomenclature for Clethodim and Metabolites of Interest.	
	propyl]-3,5-dihydroxy-2-cyclohexen-1-one]
Molecular weight	407.92 g/mol
	

3.2 Physical/Chemical Properties

Table 3.2.1 is a summary of the physical/chemical properties for clethodim.

Table 3.2.1. Physicochemical Properties of the Technical Grade Test Compound.		
Parameter	Value	Reference (MRID#)
Melting point/range	Not applicable	
Boiling point/range	Decomposes below boiling point.	46124103
pH	4.1[1,2]	46124103
Specific gravity	1.14 [1]g/mL at 20°C	46124103
Water solubility	0.54 g/100 mL (pH 7.0) [1,2]	46124103
Solvent solubility	> 90 g/100 mL in most solvents	46124103
Vapor pressure at 20°C	<1 x 10^{-2} mPa[1] at 20°C	46124103
Octanol/water partition coefficient log (K_{OW})	4.51 (21°C)	-- [3]
UV/visible absorption spectrum	Not Available	--

[1] From "Product Chemistry Review of Clethodim Technical," Shyam B. Mathur, PhD, 6/29/04, DP# 297251, US EPA Registration No. 51036-UEI.
[2] The value of this parameter was reported in the MRID without specifying a temperature of testing.
[3] S.T. Ha (1994) Determinations of Octanol/Water Partition Coefficients of Clethodim, Clethodim Sulfone, Clethodim Imine Sulfone and Clethodim Oxazole Sulfone By Reversed-Phase High Performance Liquid Chromatography, Valent U.S.A. Corporation, Project No. 10768.

3.3 Pesticide Use Pattern/Directions

Proposed Use: IR-4 has submitted proposed use directions for V-10137 1 EC Herbicide (also known as Select Max Herbicide) (EPA Reg. No. 56939-132; 0.97 lb ai per gallon formulated as a EC) and Select 2 EC Herbicide (EPA Reg. No. 56939-3; 2.0 lb ai per gallon formulated as a EC) which include instructions for applications to tree nuts and okra. For tree nuts, up to 4 applications may be made at 0.09 to 0.125 lb ai/A for control of annual and perennial grasses. A RTI of 14 days between application and a PHI of 14 days are specified. A maximum of 0.5 lb ai/A may be applied per crop year. The use directions for V-10137 1 EC Herbicide specify that a NIS should be included in the spray. The directions for Select 2 EC Herbicide specify that a COC should be included in the spray.

For okra, up to 4 applications may be made at 0.09 to 0.125 lb ai/A for control of annual and perennial grasses. A RTI of 14 days between applications and a PHI of 3 days is specified. A maximum of 0.5 lb ai/A may be applied per crop year. The use directions for V-10137 1 EC Herbicide specify that a NIS should be included in the spray. The directions for Select 2 EC Herbicide specify that a COC should be included in the spray.

The proposed application scenarios are supported by the submitted residue chemistry data.

Table 3.3.1. Summary of End-Use Product.

Trade Name	Conc.	Formulation	Label Date	Target Crops	Target Pests
V-10137 1 EC Herbicide (also known as Select Max Herbicide)	0.97 lb ai/gal	EC	07/29/2016 (date of cover letter)	Tree Nuts, Group 14-12	Annual and perennial grasses
				Okra	Annual and perennial grasses
Select 2 EC Herbicide	2.0 lb ai/gal	EC	07/29/2016 (date of cover letter)	Tree Nuts, Group 14-12	Annual and perennial grasses
				Okra	Annual and perennial grasses

Table 3.3.2. Summary of Proposed Use Directions.

App. Timing; Type; and Equip.	Formulation	Single App. Rate	Max. # App. per Season	Max. Seasonal App. Rate	PHI (days)	Use Directions and Limitations
Tree Nuts, Group 14-12						
Not specified/ Ground or aerial equipment	EC (0.97 lb ai/gallon)	9 to 16 fl. oz./A for annual grasses (0.068 to 0.121 lb ai/A) 12 to 16 fl. oz./A for perennial grasses (0.091 to 0.121 lb ai/A)	4	64 fl. oz./A (0.485 lb ai/A)	14	Apply in a minimum of 5-10 gallons per acre (GPA) for ground applications or a minimum of 3 GPA for aerial applications. Application intervals should be no shorter than 14 days. Do make more than 4 applications per year at the 16 fl. oz. rate. Do not apply more than 64 fl. oz./A per year per crop (0.485 lb ai/A per year). Include a NIS at a rate of 0.25% v/v in the finished spray volume.
Not specified/ Ground or aerial equipment	EC (2.0 lb ai/gallon)	6 to 8 fl. oz./A for annual and perennial grasses (0.09 to 0.125 lb ai/A)	4	32 fl. oz./A (0.5 lb ai/A)	14	Apply in a minimum of 5-10 GPA for ground applications or a minimum of 3 GPA for aerial applications. Application intervals should be no shorter than 14 days. Do make more than 4 applications per year at the 8 fl. oz rate. Do not apply more than 32 fl. oz./A per year per crop (0.5 lb ai/A per year). Include a COC at a rate of 1% v/v in the finished spray volume.
Okra						
Not specified/ Ground or aerial equipment	EC (0.97 lb ai/gallon)	9 to 16 fl. oz./A for annual grasses (0.068 to 0.121 lb ai/A) 12 to 16 fl. oz/A for perennial grasses (0.091 to 0.121 lb ai/A)	4	64 fl. oz./A (0.485 lb ai/A)	3	Apply in a minimum of 5-10 GPA for ground applications or a minimum of 3 GPA for aerial applications. Application intervals should be no shorter than 14 days. Do make more than 4 applications per year at the 16 fl. oz. rate. Do not apply more than 64 fl. oz./A per year per crop (0.485 lb ai/A per year). Include a nonionic surfactant at a rate of 0.25% v/v in the finished spray volume.
Not specified/ Ground or aerial equipment	EC (2.0 lb ai/gallon)	6 to 8 fl. oz./A for annual and perennial grasses (0.09 to 0.125 lb ai/A)	4	32 fl. oz./A (0.5 lb ai/A)	3	Apply in a minimum of 5-10 GPA for ground applications or a minimum of 3 GPA for aerial applications. Application intervals should be no shorter than 14 days. Do make more than 4 applications per year at the 8 fl. oz. rate. Do not apply more than 32 fl. oz./A per year per crop (0.5 lb ai/A per year). Include a crop oil concentrate at a rate of 1% v/v in the finished spray volume.

Use directions for fruiting vegetables, group 8-10, asparagus, head and stem, *Brassica*, subgroup 5A, leafy greens, *Brassica*, subgroup 5B, leafy petioles, subgroup 4B, leafy greens, subgroup 5B, and onion, green, subgroup 3-07B appear on the labels for V-10137 1 EC Herbicide (also known as Select Max Herbicide) (EPA Reg. No. 56939-132) and Select 2 EC Herbicide (EPA Reg. No. 56939-3; 2.0 lb ai per gallon formulated as a EC). The use directions for fruiting vegetables now

indicate the directions apply to fruiting vegetables except okra and tomato, group 8-10; however, tomatoes are included in the list of crops clethodim may be applied to.

Use directions for asparagus have been expanded to include all commodities of the stalk and stem vegetable, subgroup 22A. Asparagus is the representative commodity for the stalk and stem vegetable, subgroup 22A. Use directions for head and stem, *Brassica*, subgroup 5A have been expanded to include all commodities of the *Brassica* head and stem, group 5-16. Use directions for leafy greens, *Brassica*, subgroup 5B have been expanded to include all commodities of the *Brassica* leafy greens, subgroup 4-16B. Use directions for leafy petioles, subgroup 4B have been expanded to include all of the commodities of the leaf petiole vegetable, subgroup 22B. Use directions for leafy greens, subgroup 5B have been expanded to include all of the commodities of the leafy greens, subgroup 4-16A. Use directions for green onion have been expanded to include all of the commodities of the green onion, subgroup 3-07B. Green onions are the representative commodity for the green onion, subgroup 3-07B.

Conclusions: A revised Section B/proposed use is required. The use directions for fruiting vegetables, except okra and tomato, group 8-10 on the Select 2 EC label and V-10137 1 EC need to be modified to indicate the use directions apply to fruiting vegetables, except okra, group 8-10.

4.0 Metabolism/Degradate Residue Profile

References: Memo, 04/13/2016, M. Negussie, D431225
MRID 49527101
MRID 49527102

Table 4.0.7 and the following text are summaries of the residues of concern in plants (primary and rotational crops), poultry, and ruminants. For chemical structures see Attachment 2.
Note: MRID 49527101 & 49527102 were submitted as 6(a)2 data.

Summary of Submitted Metabolism Data (MRID 49527101): Arysta LifeScience Corporation has submitted a study investigating the metabolism of ring-labeled [4,6-cyclohexen-^{14}C]clethodim and [allyl-2-^{14}C]clethodim following foliar application to carrot. The radiolabeled test substances were formulated as soluble concentrate (SC) formulations and applied to carrots in outdoor plots as a single foliar broadcast application at 0.557-0.569 lb ai/A (624-638 g ai/ha). Carrots were harvested at PHIs of 21 (immature) and 56 days (mature) and separated into roots and tops. The in-life phase of the study was conducted by Excel Research Services (Fresno, CA), and the analytical phase of the study was conducted by PTRL West, Inc. (Hercules CA).

Total radioactive residues (TRR) were determined by combustion/liquid scintillation counting (LSC) and by summing extractable and nonextractable radioactivity. The summed TRR in ring-label carrot matrices were: 5.714 and 0.815 ppm in immature tops and roots and 0.842 and 0.158 ppm in mature tops and roots. The summed TRR in allyl-label matrices were: 3.888 and 0.738 ppm in immature tops and roots and 0.752 and 0.131 ppm in mature tops and roots. Surface rinses of the roots with water removed 0.066-0.093 ppm from immature roots and 0.003-0.007 ppm from mature roots.

Extraction with acetonitrile (ACN)/water released the majority of the radioactivity from immature and mature carrot matrices: 83.4-87.1% TRR for ring-label carrots and 70.9-77.1% TRR for allyl-label carrots. Sequential extraction with ACN, ACN/0.2 N hydrochloric acid (HCl), and ACN/0.2 N ammonium hydroxide (NH_4OH) released minor amounts of radioactivity

(≤3.8% TRR for any solvent in any matrix) as did sequential hydrolysis of the remaining nonextractable residues for all matrices except ring-label mature root with 0.05 M ethylenediaminetetraacetic acid (EDTA) and 1 N HCl (≤4.9% TRR). Final hydrolysis with 24% potassium hydroxide (KOH, at ambient temperature, overnight) released 3.3-7.5% TRR from ring-label matrices and 7.2-10.8% TRR from allyl-label matrices. Attempts to further investigate this hydrolysate by partitioning with dichloromethane (DCM) under acidic and basic conditions were unsuccessful. The nonextractable residues remaining following extraction and hydrolysis procedures were: 0.7% TRR (0.038 ppm) and 1.6% TRR (0.013 ppm) in immature ring-label tops and roots; 1.0% TRR (0.008 ppm) and 8.2% TRR (0.013 ppm) in mature ring-label tops and roots; 2.1% TRR (0.080 ppm) and 2.7% TRR (0.020 ppm) in immature allyl-label tops and roots; and 2.3% TRR (0.017 ppm) and 2.3% TRR (0.003 ppm) in mature allyl-label tops and roots. These procedures adequately extracted the majority of residues from all carrot matrices. Extraction results were normalized; therefore, accountabilities were ~100%.

Residues were quantified and parent and the clethodim sulfoxide and sulfone metabolites were identified in the ACN/water extracts of carrot matrices by high performance liquid chromatography with UV detection (HPLC/UV). Identification of clethodim sulfoxide and clethodim sulfone was confirmed by thin layer co-chromatography (TLC). Remaining metabolites were identified or tentatively identified by high performance liquid chromatography with tandem mass spectrometry detection (LC/MS/MS) in conjunction with HPLC co-chromatography for certain metabolites. Samples of immature and mature carrot tops and roots were stored frozen (~-20 °C) and were initially analyzed within 40-42 days (1.3-1.4 months) of harvest. Based on dated chromatograms, LC/MS/MS analyses of immature foliage extracts were completed within 228 days (7.5 months) of harvest. Repeat HPLC analysis of the ACN/water extracts of immature tops conducted within 216 days (7.1 months) of harvest indicated that the metabolite profile was generally stable during frozen storage. No additional storage stability data are required to support the study.

Clethodim was a minor residue component identified in the ACN/water extracts of immature tops and roots only (both labels) at <0.1-0.2% TRR. Clethodim sulfoxide was the major identified residue component in all matrices (both labels), accounting for 11.3-11.8% TRR (0.095-0.663 ppm) and 16.2-18.4% TRR (0.029-0.132 ppm) in ring-label tops and roots, respectively, and for 19.4-21.7% TRR (0.164-0.757 ppm) and 22.1-24.4% TRR (0.032-0.163 ppm) in allyl-label tops and roots, respectively. Clethodim sulfone was also identified at slightly higher levels in roots than in tops for both labels: at 3.2-4.8% and 6.3-7.0% TRR in ring-label tops and roots, and at 6.0-6.1% and 7.7-9.9% TRR in allyl-label tops and roots. In ring-label carrots, five additional metabolites were identified or tentatively identified as major residue components in one or more matrices: (1) dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R) in all matrices at 3.6-12.0% TRR (0.019-0.594 ppm); (2) 3-[(2-ethylsulfinyl)propyl]-pentanedioic acid (M17R) in all matrices at 8.9-13.9% TRR (0.022-0.519 ppm); (3) 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid (M18R) in all matrices at 7.3-12.7% TRR (0.020-0.410 ppm); (4) an imine glucose conjugate (M19R) in immature and mature tops at 11.2-14.1% TRR (0.119-0.633 ppm); and (5) an imine sulfoxide and hydroxy imine sulfoxide metabolite pair (M22R) in immature tops only at 12.6% TRR (0.710 ppm). Two additional metabolites were tentatively identified in immature and mature tops only: imine sulfone (M24R) at 6.5-7.4% TRR (0.062-0.369 ppm) and clethodim sulfoxide glucoside (M26) at 6.4-9.3% TRR (0.078-0.360 ppm). Clethodim sulfoxide glucoside (M26) was the only metabolite, other than clethodim sulfoxide and sulfone, that was also identified in allyl-label matrices, where it accounted for 9.9-14.6% TRR (0.111-0.385 ppm) in immature and mature tops. Remaining metabolites identified

in allyl-label matrices were minor components: a 3-chloroallyl glucoside (M15A) at 3.1-6.5% TRR in all matrices; and 2-(glutamyl-cysteinyl)-3-chloracrylic acid (M22A) at 7.3% TRR in immature and mature tops only. A highly polar, acidic metabolite (M3A) was a major residue component (11.0-15.3% TRR, 0.020-0.081 ppm) in allyl-label roots; less radioactivity eluted with this fraction in ring-label carrot and was not investigated. No structure was proposed for M3A. Remaining discrete unknowns accounted for 2.8-10.1% TRR in ring-label carrot matrices (0.016-0.157 ppm; two unknowns, none >6.3% TRR) and for 12.9-17.2% TRR (0.130-0.501 ppm; four unknowns, none >7.0% TRR) in allyl-label tops and 4.3-8.4% TRR (0.011-0.032 ppm; two unknowns, none >6.1% TRR) in allyl-label roots. As noted above, remaining extraction/hydrolysis procedures released minor amounts of radioactivity except for hydrolysis with 24% KOH.

Based on the results of the carrot metabolism study, the petitioner concluded that clethodim was metabolized extensively in carrot, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring.

The distribution of radioactivity in carrot tops and roots is presented in Tables 4.0.1. (ring label) and 4.0.2. (allyl label).

Ring label:

Table 4.0.1. Distribution of Clethodim and Its Metabolites in Carrot Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.569 lb ai/A (638 g ai/ha).[1]

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =5.714 ppm)		(TRR = 0.815 ppm)		(TRR = 0.842 ppm)		(TRR = 0.158 ppm)	
	%TRR	Ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	87.1	4.978	84.4	0.688	83.4	0.702	86.7	0.137
Clethodim	<0.1	0.004	0.2	0.002	--	--	--	--
Clethodim sulfoxide (total)[2]	11.8	0.663	16.2	0.132	11.3	0.095	18.4	0.029
Clethodim sulfoxide (M29)	4.7	0.264	5.0	0.041	7.4	0.062	7.6	0.012
Clethodim sulfoxide (M37)	7.1	0.399	11.2	0.091	3.9	0.033	10.8	0.017
Clethodim sulfone (total)[2]	3.2	0.180	6.3	0.051	4.8	0.040	7.0	0.011
Clethodim sulfone (M33)	1.9	0.109	3.8	0.031	3.7	0.031	5.1	0.008
Clethodim sulfone (M41)	1.3	0.071	2.5	0.020	1.1	0.009	1.9	0.003
Dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R)	10.5	0.594	7.7	0.063	3.6	0.030	12.0	0.019
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M17R)	9.2	0.519	13.1	0.107	8.9	0.075	13.9	0.022
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M18R)	7.3	0.410	8.8	0.072	8.1	0.068	12.7	0.020
Imine glucose conjugate (M19R)	11.2	0.633	--	--	14.1	0.119	--	--
Clethodim Imine sulfoxide and hydroxy imine sulfoxide (M22R)	12.6	0.710	--	--	--	--	--	--
Clethodim imine sulfone (M24R)	6.5	0.369	--	--	7.4	0.062	--	--
Clethodim sulfoxide glucoside (M26)	6.4	0.360	--	--	9.3	0.078	--	--
Unknown M3R	0.4	0.024	2.5	0.020	0.4	0.003	3.8	0.006
Unknown M27	2.4	0.133	3.2	0.026	3.1	0.026	6.3	0.010
CAN	1.0	0.057	2.9	0.024	1.3	0.011	3.8	0.006
ACN/0.2 N HCl	1.2	0.066	1.7	0.014	2.0	0.017	1.3	0.002
ACN/0.2 N NH_4OH	1.9	0.109	2.5	0.020	1.9	0.016		

Table 4.0.1. Distribution of Clethodim and Its Metabolites in Carrot Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.569 lb ai/A (638 g ai/ha).[1]

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =5.714 ppm)		(TRR = 0.815 ppm)		(TRR = 0.842 ppm)		(TRR = 0.158 ppm)	
	%TRR	Ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
0.05 M EDTA	1.5	0.085	1.5	0.012	1.3	0.011		
1 N HCl	1.8	0.101	2.0	0.016	1.5	0.013		
24% KOH	4.8	0.276	3.3	0.027	7.5	0.063		
DCM (pH 14)	<0.1	0.001	<0.1	<<0.001	<0.1	<<0.001		
DCM (pH 2)	0.1	0.003	<0.1	<<0.001	0.2	0.001		
Aqueous	3.6	0.203	3.2	0.026	7.3	0.061		
24% KOH filter paper	0.1	0.004	0.1	0.001	0.1	0.001		
Nonextractable	0.7	0.038	1.6	0.013	1.0	0.008	8.2	0.013

[1] Blank spaces indicate that the extraction step and/or characterization analysis was not conducted for the fraction in question.
[2] Residues of clethodim sulfoxide and clethodim sulfone eluted in two peaks as the result of *syn/anti* inter-conversion of oxime ethers. Total values were calculated by the petitioner by summing the individual fractions.

Allyl label:

Table 4.0.2. Distribution of the Clethodim and Its Metabolites in Carrot Matrices Following Application of [allyl-2-^{14}C]Clethodim at 0.557 lb ai/A (624 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =3.888 ppm)		(TRR = 0.738 ppm)		(TRR =0.752 ppm)		(TRR = 0.131 ppm)	
	%TRR	Ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	76.1	2.960	70.9	0.523	74.7	0.562	77.1	0.101
Clethodim	0.1	0.005	0.1	0.001	--	--	--	--
Clethodim sulfoxide (total)[1]	19.4	0.757	22.1	0.163	21.7	0.164	24.4	0.032
Clethodim sulfoxide (M29)	7.3	0.285	7.2	0.053	9.5	0.072	7.6	0.010
Clethodim sulfoxide (M37)	12.1	0.472	14.9	0.110	12.2	0.092	16.8	0.022
Clethodim sulfone (total)[1]	6.1	0.234	7.7	0.057	6.0	0.046	9.9	0.013
Clethodim sulfone (M33)	4.0	0.154	5.0	0.037	3.4	0.026	6.1	0.008
Clethodim sulfone (M41)	2.1	0.080	2.7	0.020	2.6	0.020	3.8	0.005
3-chloroallyl alcohol glucoside (M15A)	4.8	0.185	6.5	0.048	3.6	0.027	3.1	0.004
2-(Glutamyl-cysteinyl)-3-chloroacrylic acid (M22A)	7.3	0.282	--	--	7.3	0.055	--	--
Clethodim sulfoxide glucoside (M26)	9.9	0.385	--	--	14.6	0.111	--	--
Unknown M3A (polar, acidic)	3.2	0.124	11.0	0.081	0.8	0.006	15.3	0.020
Unknown M17A	--	--	0.9	0.007	--	--	6.1	0.008
Unknown M18A	0.6	0.024	--	--	--	--	--	--
Unknown M19A	4.6	0.177	--	--	4.5	0.034	--	--
Unknown M24A	1.9	0.075	--	--	5.7	0.043	--	--
Unknown M27	5.8	0.225	3.4	0.025	7.0	0.053	2.3	0.003
CAN	1.9	0.073	3.8	0.028	2.9	0.022	3.1	0.004
ACN/0.2 N HCl	2.9	0.112	3.7	0.027	2.3	0.017	2.3	0.003
ACN/0.2 N NH_4OH	2.7	0.105	3.7	0.027	1.9	0.014	1.5	0.002
0.05 M EDTA	2.1	0.081	2.8	0.021	1.5	0.011	<0.1	<0.001
1 N HCl	4.0	0.157	4.9	0.036	3.2	0.024	3.8	0.005
24% KOH	8.2	0.319	7.2	0.053	10.8	0.081	9.9	0.013
DCM (pH 14)	0.2	0.009	0.3	0.002	0.3	0.002	0.3	<<0.001
DCM (pH 2)	0.2	0.010	0.3	0.002	0.3	0.003	0.7	0.001
Aqueous	7.7	0.300	6.6	0.049	10.6	0.080	8.9	0.012
24% KOH filter paper	<0.1	0.001	0.4	0.003	0.5	0.004	0.8	0.001
Nonextractable	2.1	0.080	2.7	0.020	2.3	0.017	2.3	0.003

[1] Residues of clethodim sulfoxide and clethodim sulfone eluted in two peaks as the result of *syn/anti* inter-conversion of oxime ethers. Total values were calculated by the petitioner by summing the individual fractions.

The characterization and identification of radioactivity in carrot tops and roots is presented in Tables 4.0.3. (ring label) and 4.0.4. (allyl label).

Ring label:

Table 4.0.3. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.569 lb ai/A (638 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR = 5.714 ppm)		(TRR = 0.815 ppm)		(TRR = 0.842 ppm)		(TRR = 0.158 ppm)	
	%TRR	Ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Clethodim	<0.1	0.004	0.2	0.002	--	--	--	--
Clethodim sulfoxide	11.8	0.663	16.2	0.132	11.3	0.095	18.4	0.029
Clethodim sulfone	3.2	0.180	6.3	0.051	4.8	0.040	7.0	0.011
Dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R)	10.5	0.594	7.7	0.063	3.6	0.030	12.0	0.019
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M17R)	9.2	0.519	13.1	0.107	8.9	0.075	13.9	0.022
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M18R)	7.3	0.410	8.8	0.072	8.1	0.068	12.7	0.020
Imine glucose conjugate (M19R)	11.2	0.633	--	--	14.1	0.119	--	--
Clethodim imine sulfoxide and hydroxy imine sulfoxide (M22R)	12.6	0.710	--	--	--	--	--	--
Clethodim imine sulfone (M24R)	6.5	0.369	--	--	7.4	0.062	--	--
Clethodim sulfoxide glucoside (M26)	6.4	0.360	--	--	9.3	0.078	--	--
Unknown M3R	0.4	0.024	2.5	0.020	0.4	0.003	3.8	0.006
Unknown M27	2.4	0.133	3.2	0.026	3.1	0.026	6.3	0.010
ACN	1.0	0.057	2.9	0.024	1.3	0.011	3.8	0.006
ACN/0.2 N HCl	1.2	0.066	1.7	0.014	2.0	0.017	1.3	0.002
ACN/0.2 N NH_4OH	1.9	0.109	2.5	0.020	1.9	0.016	--	--
0.05 M EDTA	1.5	0.085	1.5	0.012	1.3	0.011	--	--
1 N HCl	1.8	0.101	2.0	0.016	1.5	0.013	--	--
24% KOH	4.8	0.276	3.3	0.027	7.5	0.063	--	--
24% KOH filter paper	0.1	0.004	0.1	0.001	0.1	0.001	--	--
Total extractable	99.4	5.676	98.4	0.802	99.0	0.834	91.8	0.145
Total identified	<78.8	4.442	52.3	0.427	67.5	0.567	64.0	0.101
Total unidentified	15.1	0.855	19.7	0.160	19.1	0.161	15.2	0.024
Total bound residues (PES)[1]	0.7	0.038	1.6	0.013	1.0	0.008	8.2	0.013
% Accountability[2]	100		100		100		100	

[1] PES = Post-extraction solids.
[2] Total (ppm)/TRR (ppm)*100

Allyl label:

Table 4.0.4. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [allyl-2-^{14}C]Clethodim at 0.557 lb ai/A (624 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =3.888 ppm)		(TRR = 0.738 ppm)		(TRR =0.752 ppm)		(TRR = 0.131 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Clethodim	0.1	0.005	0.1	0.001	--	--	--	--
Clethodim sulfoxide	19.4	0.757	22.1	0.163	21.7	0.164	24.4	0.032
Clethodim sulfone	6.1	0.234	7.7	0.057	6.0	0.046	9.9	0.013

Table 4.0.4. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [allyl-2-^{14}C]Clethodim at 0.557 lb ai/A (624 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =3.888 ppm)		(TRR = 0.738 ppm)		(TRR =0.752 ppm)		(TRR = 0.131 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
3-chloroallyl alcohol glucoside (M15A)	4.8	0.185	6.5	0.048	3.6	0.027	3.1	0.004
2-(Glutamyl-cysteinyl)-3-chloroacrylic acid (M22A)	7.3	0.282	--	--	7.3	0.055	--	--
Clethodim sulfoxide glucoside (M26)	9.9	0.385	--	--	14.6	0.111	--	--
Unknown M3A (polar, acidic)	3.2	0.124	11.0	0.081	0.8	0.006	15.3	0.020
Unknown M17A	--	--	0.9	0.007	--	--	6.1	0.008
Unknown M18A	0.6	0.024	--	--	--	--	--	--
Unknown M19A	4.6	0.177	--	--	4.5	0.034	--	--
Unknown M24A	1.9	0.075	--	--	5.7	0.043	--	--
Unknown M27	5.8	0.225	3.4	0.025	7.0	0.053	2.3	0.003
CAN	1.9	0.073	3.8	0.028	2.9	0.022	3.1	0.004
ACN/0.2 N HCl	2.9	0.112	3.7	0.027	2.3	0.017	2.3	0.003
ACN/0.2 N NH_4OH	2.7	0.105	3.7	0.027	1.9	0.014	1.5	0.002
0.05 M EDTA	2.1	0.081	2.8	0.021	1.5	0.011	<0.1	<0.001
1 N HCl	4.0	0.157	4.9	0.036	3.2	0.024	3.8	0.005
24% KOH	8.2	0.319	7.2	0.053	10.8	0.081	9.9	0.013
24% KOH filter paper	<0.1	0.001	0.4	0.003	0.5	0.004	0.8	0.001
Total extractable	98.0	3.808	97.4	0.718	97.8	0.735	98.5	0.129
Total identified	47.6	1.848	36.4	0.269	53.2	0.403	37.4	0.049
Total unidentified	38.0	1.473	41.8	0.308	41.1	0.309	45.2	0.060
Total bound residues (PES)[1]	2.1	0.080	2.7	0.020	2.3	0.017	2.3	0.003
% Accountability[2]	100		100		100		101	

[1] PES = post-extraction solids.
[2] Total (ppm)/TRR (ppm)*100

Summary of Submitted Metabolism Data (MRID 49527102): Arysta LifeScience Corporation has submitted a study investigating the metabolism of ring-labeled [4,6-cyclohexen-^{14}C]clethodim (ring-label) and [allyl-2-^{14}C]clethodim (allyl-label)following foliar application to spinach. The radiolabeled test substances were formulated as SC formulations and applied to spinach in outdoor plots as a single foliar broadcast application at 0.481-0.508 lb ai/A (539-569 g ai/ha). Spinach was harvested at PHIs of 14 and 28 days. The in-life phase of the study was conducted by Excel Research Services (Fresno, CA), and the analytical phase of the study was conducted by PTRL West, Inc. (Hercules CA).

TRR were determined by combustion/LSC and by summing extractable and nonextractable radioactivity. The summed TRR in spinach matrices were: 6.848 and 3.352 ppm in immature and mature ring-label spinach and 5.158 and 3.459 ppm in immature and mature allyl-label spinach.

Extraction with ACN/water released the majority of the radioactivity from immature and mature spinach matrices: 89.9-90.2% TRR for ring-label spinach and 75.3-76.7% TRR for allyl-label spinach. Sequential extraction with ACN, ACN/0.2 N HCl, and ACN/0.2 N NH_4OH released minor amounts of radioactivity (≤2.9% TRR for any solvent in any matrix). Sequential hydrolysis of the remaining nonextractable residues with 1 N HCl and 24% KOH released an additional 5.3-5.9% TRR from ring-label spinach and 14.0-15.1% TRR from allyl-label spinach. Attempts to further investigate the 24% KOH hydrolysate by partitioning with DCM under

acidic and basic conditions were unsuccessful. The nonextractable residues remaining following extraction and hydrolysis procedures were: 0.4-0.5% TRR (0.014-0.034 ppm) in immature and mature ring-label spinach, and 2.1% TRR (0.074-0.108 ppm) in immature and mature allyl-label spinach. These procedures adequately extracted the majority of residues from all spinach matrices. Extraction results were normalized; therefore, accountabilities were ~100%.

Residues were quantified and the clethodim sulfoxide and sulfone metabolites were identified in the ACN/water extracts of spinach by HPLC/UV. Identification of clethodim sulfoxide, clethodim sulfone, and clethodim imine sulfoxide was confirmed by TLC. Remaining metabolites were identified or tentatively identified by LC/MS/MS in conjunction with HPLC co-chromatography for certain metabolites. In addition, chromatography results were compared to those of the associated carrot metabolism study (refer to MRID 49527101). Samples of immature and mature spinach were stored frozen (~-20 °C) for 35-60 days (1.2-2.0 months) prior to definitive HPLC analysis. Based on dated chromatograms, LC/MS analyses of isolated metabolites may have been completed within 314 days (10.3 months) of harvest. To demonstrate the stability of the residue profile during storage, the ACN/water extracts of all matrices were re-analyzed 256-270 days (8.4-8.9 months) after harvest. Comparison of the chromatograms suggests the metabolite profile was generally stable during frozen storage, although there were some changes in the relative amounts of certain metabolites. No additional storage stability data are required to support the study.

Clethodim was not identified in any spinach sample. Clethodim sulfoxide was identified at 2.8-3.6% TRR in ring-label spinach and at 4.7-5.1% TRR in allyl-label spinach, and clethodim sulfone was identified at 0.3-0.6% TRR in immature (both labels) and mature (allyl-label) spinach. The major residue components in ring-label spinach were: (1) hydroxy 3-[(2-ethylsulfinyl)propyl]pentanedioic acid (M14R) at 12.8-14.2% TRR (0.476-0.875 ppm); (2) 3-[(2-ethylsulfinyl)propyl]pentanedioic acid (M16R/M17R) at 33.3-34.6% TRR (1.158-2.280 ppm); (3) 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid (M19R) at 9.7-12.5% TRR (0.418-0.663 ppm); and (4) an imine sulfone and hydroxy imine sulfone glucoside pair (M20R) at 9.2% TRR (0.308 ppm, mature only); (5) clethodim imine sulfoxide (M21R) at 14.3% TRR (0.979 ppm, immature only), and clethodim imine sulfone (M23R) at 6.3-7.5% TRR (0.251-0.430 ppm). Clethodim sulfoxide glucoside (M26R/M26A) was a minor residue component (≤3% TRR) in spinach from both labels. In allyl-label spinach, the major identified residue component was 3-chloroallyl glucoside (M14A/M15A) at 21.2-22.7% TRR (0.785-1.089 ppm), and the only other identified metabolite was 2-(glutamyl-cysteinyl)-3-chloropropanol (M19A) at 6.8-9.5% TRR (0.327-0.352 ppm). A highly polar, acidic metabolite (M3/4A) was a major residue component (17.5-21.0% TRR, 0.726-0.903 ppm) in allyl-label spinach. No structure was proposed for this metabolite. Remaining discrete unknowns accounted for 6.8-7.8% TRR in ring-label matrices and 6.1-14.1% TRR in allyl-label matrices (none present at >3.9% TRR).

Based on the results of the spinach metabolism study, the petitioner concluded that clethodim was metabolized extensively in spinach, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring. The study results indicated that metabolism of clethodim in spinach was very similar to that observed in carrot.

The distribution of radioactivity in spinach is presented in Table 4.0.5.

Table 4.0.5. Distribution of the Clethodim and Its Metabolites in Spinach Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.481 lb ai/A (539 g ai/ha) or [allyl-2-^{14}C]Clethodim at 0.508 lb ai/A (569 g ai/ha).

Metabolite Fraction	Ring label				Allyl label			
	Immature		Mature		Immature		Mature	
	(TRR =6.848 ppm)		(TRR = 3.352 ppm)		(TRR = 5.158 ppm)		(TRR = 3.459 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	89.9	6.156	90.2	3.023	75.3	3.882	76.7	2.654
Clethodim sulfoxide (total)[1]	2.8	0.191	3.6	0.119	5.1	0.262	4.7	0.162
Clethodim sulfoxide (M28)	1.9	0.127	3.6	0.119	3.8	0.196	3.4	0.119
Clethodim sulfoxide (M37)	0.9	0.064	--	--	3.0	0.154	1.2	0.043
Clethodim sulfone (M42)[1]	0.3	0.019	--	--	0.6	0.031	0.3	0.010
Hydroxy 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M14R)	12.8	0.875	14.2	0.476	--	--	--2	--
3-Chloroallyl alcohol glucoside, alpha anomer (M14A)	--	--	--	--	5.7	0.292	15.1	0.521
3-Chloroallyl alcohol glucoside, beta anomer (M15A)	--	--	--	--	15.5	0.797	7.6	0.264
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid, diastereomer (M16R)	20.5	1.402	15.5	0.519	--	--	--	--
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid, diasteromer (M17R)	12.8	0.878	19.1	0.639	--	--	--	--
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M19R)	9.7	0.663	12.5	0.418	--	--	--	--
2-(Glutamyl-cysteinyl)-3-chloropropanol (M19A)	--	--	--	--	6.8	0.352	9.5	0.327
Clethodim imine sulfone and hydroxy imine sulfone glucoside (M20R)	--	--	9.2	0.308	--	--	--	--
Clethodim imine sulfoxide (M21R)	14.3	0.979	--	--	--	--	--	--
Clethodim imine sulfone (M23R)	6.3	0.430	7.5	0.251	--	--	--	--
Clethodim sulfoxide glucoside (M26R/M26A)	1.6	0.108	1.6	0.053	--	--	3.0	0.103
Unknown M3R	0.6	0.040	1.6	0.055	--	--	--	--
Unknown M3/4A	--	--	--	--	17.5	0.903	21.0	0.726
Unknowns M10R/M10A	1.3	0.089	0.5	0.017	1.9	0.098	--	--
Unknown M17A	--	--	--	--	--	--	1.9	0.066
Unknown M18A	--	--	--	--	2.2	0.114	--	--
Unknown M20A	--	--	--	--	2.2	0.112	--	--
Unknowns M25R/M25A	3.1	0.212	2.7	0.087	3.8	0.196	2.9	0.099
Unknowns M27R/M27A	1.4	0.096	1.3	0.045	3.9	0.203	--	--
Unknowns M32R/M32A	1.4	0.093	0.7	0.024	0.1	0.004	1.3	0.046
ACN	1.3	0.090	0.5	0.017	2.7	0.137	2.3	0.078
ACN/0.2 N HCl	1.7	0.119	1.2	0.040	2.9	0.151	2.8	0.096
ACN/0.2 N NH_4OH	1.3	0.086	1.8	0.061	2.0	0.101	1.8	0.061
1 N HCl	3.2	0.216	2.6	0.087	9.2	0.473	8.9	0.307
24% KOH	2.1	0.146	3.3	0.110	5.9	0.306	5.1	0.176
DCM (pH 14)	0.1	0.004	0.1	0.002	0.1	0.004	0.1	0.003
DCM (pH 2)	0.1	0.008	0.1	0.005	0.1	0.005	0.1	0.002
Aqueous	2.0	0.135	3.0	0.102	5.8	0.298	4.9	0.170
Nonextractable	0.5	0.034	0.4	0.014	2.1	0.108	2.1	0.074

[1] Residues of clethodim sulfoxide and clethodim sulfone eluted in two peaks as the result of *syn/anti* inter-conversion of oxime ethers. For clethodim sulfone only results for the major isomer were reported. Total values for clethodim sulfoxide were calculated by the petitioner by summing the individual fractions.

The characterization and identification of radioactivity in spinach is presented in Table 4.0.6.

Table 4.0.6. Summary of Characterization and Identification of Radioactive Residues in Spinach Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.481 lb ai/A (539 g ai/ha) or [allyl-2-^{14}C]Clethodim at 0.508 lb ai/A (569 g ai/ha) .

Metabolite Fraction	Ring label				Allyl label			
	Immature		Mature		Immature		Mature	
	(TRR =6.848 ppm)		(TRR = 3.352 ppm)		(TRR = 5.158 ppm)		(TRR = 3.459 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	Ppm
Clethodim sulfoxide	2.8	0.191	3.6	0.119	5.1	0.262	4.7	0.162
Clethodim sulfone	0.3	0.019	--	--	0.6	0.031	0.3	0.010
Hydroxy 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M14R)	12.8	0.875	14.2	0.476	--	--	--	--
3-Chloroallyl alcohol glucoside (M14A/M15A)	--	--	--	--	21.2	1.089	22.7	0.785
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M16R/M17R)	33.3	2.280	34.6	1.158	--	--	--	--
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M19R)	9.7	0.663	12.5	0.418	--	--	--	--
2-(Glutamyl-cysteinyl)-3-chloropropanol (M19A)	--	--	--	--	6.8	0.352	9.5	0.327
Clethodim imine sulfone and/or hydroxy imine sulfone glucoside (M20R)	--	--	9.2	0.308	--	--	--	--
Clethodim imine sulfoxide (M21R)	14.3	0.979	--	--	--	--	--	--
Clethodim imine sulfone (M23R)	6.3	0.430	7.5	0.251	--	--	--	--
Clethodim sulfoxide glucoside (M26R/M26A)	1.6	0.108	1.6	0.053	--	--	3.0	0.103
Unknown M3/4A	--	--	--	--	17.5	0.903	21.0	0.726
Minor unknowns (ea. ≤3.9% TRR)	7.8	0.530	6.8	0.228	14.1	0.727	6.1	0.211
CAN	1.3	0.090	0.5	0.017	2.7	0.137	2.3	0.078
ACN/0.2 N HCl	1.7	0.119	1.2	0.040	2.9	0.151	2.8	0.096
ACN/0.2 N NH_4OH	1.3	0.086	1.8	0.061	2.0	0.101	1.8	0.061
1 N HCl	3.2	0.216	2.6	0.087	9.2	0.473	8.9	0.307
24% KOH	2.1	0.146	3.3	0.110	5.9	0.306	5.1	0.176
Total extractable	99.5	6.813	99.6	3.338	98.0	5.050	97.6	3.372
Total identified	81.1	5.545	83.2	2.783	33.7	1.734	40.2	1.387
Total unidentified	17.4	1.187	16.2	0.543	54.3	2.798	48.0	1.655
Total bound residues (PES)[1]	0.5	0.034	0.4	0.014	2.1	0.108	2.1	0.074
% Accountability[2]	100		100		100		100	

[1] PES = post-extraction solids.
[2] Total (ppm)/TRR (ppm)*100

HED Comments: The metabolism studies were submitted to the Agency as 6(a)2 data because metabolites that do not contain the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties were identified in the submitted studies. The following metabolites do not contain the moieties: M15R, M15A, M17R & M16R, M18R, M14R, and M19A.

Table 4.0.7. Summary of Data from Carrot Studies for Metabolites that Do Not Contain the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one Moieties.

Metabolite	Immature		Mature	
	Tops (TRR = 5.714 ppm)	Roots (TRR = 0.815 ppm)	Tops (TRR = 0.842 ppm)	Root (TRR = 0.158 ppm)
M15R	10.5/0.594 (NF)	7.7/0.063 (NF)	3.6/0.030 (NF)	12.0/0.019 (NF)
M15A	NF[1] (4.8/0.185)	NF (6.5/0.048)	NF (3.6/0.027)	NF (3.1/0.004)

M17R & M16R	9.2/0.519 (NF)	13.1/0.107 (NF)	8.9/0.075 (NF)	13.9/0.022 (NF)
M18R	7.3/0.410 (NF)	8.8/0.072 (NF)	8.1/0.068 (NF)	12.7/0.020 (NF)
M14R	(NF) (NF)	NF (NF)	NF (NF)	NF (NF)
M19A	NF 4.6/0.177	NF (NF)	NF 4.5/0.034	NF (NF)

[1] %TRR/residue level. Top entry is for the ring-labeled study and the bottom entry is for the allyl-label study.
[2] NF = not found.

Table 4.0.8. Summary of Data from Spinach Studies for Metabolites that Do Not Contain the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one Moieties.

Metabolite	*Ring Label*		*Allyl Label*	
	Immature (TRR = 6.848 ppm)	Mature (TRR = 3.352 ppm)	Immature (TRR = 5.158 ppm)	Mature (TRR = 3.459 ppm)
M15R	NF	NF	NF	NF
M15A	NF	NF	21.2/1.089	22.7/0.785
M17R & M16R	33.3/2.280	34.6/1.158	NF	NF
M18R	NF	NF	NF	NF
M14R	12.8/0.875	14.2/0.476	NF	NF
M19A	NF	NF	6.8/0.352	9.5/0.327

[1] %TRR/residue level.
[2] NF = not found.

Previously submitted plant metabolism data:
References: Memo, 01/31/95, J. Morales, PP#4F4340, D203378

Metabolism studies for clethodim on carrots, soybeans, and cotton were previously submitted. The metabolism of clethodim in soybean, cotton, and carrots, including soybean seed and foliage, cotton seed and foliage, and carrot root and leaves, were found to be similar. In addition, the confined rotational crop data from carrot, wheat, and lettuce provide adequate information to define the metabolic profile across numerous crops.

The major metabolic pathways for clethodim in tested crops are initial sulfoxidation to clethodim sulfoxide (CSO) followed by further oxidation to clethodim sulfone (CSO_2). The elimination of the chloroallyloxy side chain yields the imine sulfoxide (ISO) and sulfone (ISO_2), and the hydroxylation of these compounds forms the 5-OH sulfoxide (5OH-SO) and sulfone (5OH-SO_2). Clethodim sulfoxide and clethodim sulfone conjugates were also detected as major or minor metabolites, depending on plant species and sub-fractions. Also present as a minor metabolite was the aromatic sulfone. A study designed to follow the fate of the chloroallyloxy group was done side-by-side with the ^{14}C-ring-labeled clethodim study discussed above. The results showed that the chloroallyloxy moiety which was cleaved from clethodim underwent extensive metabolism, eliminating the chlorine atom and incorporating the three carbon moieties into natural plant components (with some being evolved as $^{14}CO_2$).

Conclusions: The nature of the residue in plants is adequately understood based on the available metabolism studies on carrot, soybean, cotton, and foliage of these crops and the newly submitted studies on carrot and spinach. The metabolism studies on these crops combined with the confined rotational crop data from carrot, wheat, and lettuce provide adequate information to define the metabolic profile across numerous crops.

Based on the available data, HED determined that the residues of concern are clethodim and its

metabolites containing the 2-cyclohexen-1-one moiety; however, in order to harmonize with Codex, HED determined that the tolerance should be expressed as clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim. Additionally, the newly submitted metabolism studies do not change these conclusions.

Livestock: The nature of the residue in livestock is adequately understood based on acceptable ruminant (goat) and poultry (laying hen) metabolism studies. In the goat, the dominant metabolic process is the oxidation of clethodim to clethodim sulfoxide and, to a lesser extent, clethodim sulfone. Clethodim can also be converted to the S-methyl metabolite, which can be oxidized to S-methyl sulfoxide and S-methyl sulfone metabolites. Cleavage of the oxime N-O bond in clethodim produces the imine, which is rapidly oxidized to imine sulfoxide. In the laying hen, the metabolism of clethodim was observed to be not as complex as in the goat. The chicken tissues and eggs contained only clethodim, clethodim sulfoxide, and clethodim sulfone.

Conclusions: HED has determined that the residues of concern in meat, milk, poultry, and eggs are clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.

Based on the previously submitted metabolism data, the HED concluded that the residues of concern, for tolerance enforcement and risk assessment, are as defined in Table 4.0.9.

Table 4.0.9. Summary of Metabolites and Degradates of Concern for Risk Assessment and Tolerance Enforcement.

Matrix	Residues of Concern[1]	
	Risk Assessment	Tolerance Enforcement
Primary crops	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.
Ruminants	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.
Poultry	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.
Rotational Crops	Not applicable.	Not applicable.
Water	Clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.	NA[2]

[1] Memo, 01/31/95, J. Morales, PP#4F4340, D203378
[2] NA = not applicable.

5.0 Residue Profile

5.1 Residue Analytical Methods

5.1.1 Data-Collection Methods

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety (the residues of concern in plants) using GC/MS Method YARL-0602D, adapted from Method RM-26B-3. The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH).

Briefly, samples were first soaked in water for 1 hour, then blended with methanol; the extract was isolated by filtration after addition of a filter aid and then concentrated, brought to volume with methanol, and diluted with water. Calcium hydroxide (CaOH) was added, and the extract was allowed to stand for 30 minutes before vacuum filtration and dilution with water:methanol (2:1, v:v). Following acidification with concentrated HCl and saturation with sodium chloride, the extract was partitioned (3x) with DCM, and the combined organic layers were evaporated to dryness. A 1% aqueous barium hydroxide solution was added, the mixture was heated to reflux, and the sample was oxidized using hydrogen peroxide solution. The pH was adjusted to neutral with 2 N NaOH or 2 N HCl, then excess hydrogen peroxide was removed by the addition of catalase; the mixture was acidified to pH 4.0-4.5 using potassium pyrosulfite. Glacial acetic acid was added, and the sample was evaporated to dryness. The residue was methylated using methanol and concentrated HCl at reflux, then the pH was adjusted to >7 with sodium bicarbonate solution, and the mixture was partitioned (2x) with DCM. The combined organic phases were evaporated to dryness and dissolved in acetone for analysis by GC/MS. The ions monitored were: *m/z* 143, 167, and 175 for DME, and *m/z* 169, 137, and 263 for DME-OH. Residues were reported as clethodim equivalents using molecular weight conversion factors of 1.22 for DME and 1.16 for DME-OH.

The limit of quantitation (LOQ; determined as the lowest level of method validation, LLMV) was 0.1 ppm for DME and DME-OH in okra, almond, and pecan, which is equivalent to 0.096 and 0.088 ppm, respectively, as clethodim equivalents. Acceptable method validation and concurrent recoveries were reported for samples of okra, pecans, and almond nutmeat and hulls fortified with CSO and 5-OH CSO2 at 0.10 and 1.0 ppm, which were adequate to bracket residue levels.

5.1.2 Food and Drug Administration (FDA) Multiresidue Methods (MRMs)

Reference:
Memo, 04/13/2016, M. Negussie, D431225

The requirements for data pertaining to multiresidue methods are fulfilled. These data, which have been forwarded to FDA for review, indicate that adequate recoveries of clethodim, clethodim sulfoxide, and 5-OH clethodim sulfone have been obtained under FDA's multiresidue protocols. The FDA multiresidue methods are not adequate for enforcement of tolerances as they do not determine all of the residues of concern in plant commodities.

5.1.3 Tolerance-Enforcement Method

Reference:
Memo, 04/13/2016, M. Negussie, D431225

Adequate analytical methods are available for enforcing clethodim tolerances in/on the proposed/registered plant commodities. Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using GC/MS Method YARL-0602D, adapted from Method RM-26B-3. There are two analytical methods (RM-26B-2 and RM-26B-3) which have undergone successful petition method validations in EPA laboratories. A confirmatory method, EPA-RM-26D-2, has also been determined to be suitable for enforcement of tolerances for clethodim residues. These methods (RM-26B-2 and RM-26B-3) are adequate for enforcement of the proposed tolerances.

5.1.4 Submittal of Analytical Reference Standards

Reference:
Correspondence with G. Verdin, BEAD/ACL, 06/05/2017.

The EPA National Pesticide Standards Repository has analytical standards of clethodim with an expiration date of 04/19/2018; clethodim sulfone with an expiration date of 08/15/2018; clethodim, 5-OH sulfone with an expiration date of 09/01/2018; clethodim sulfoxide with an expiration date of 08/11/2018; and clethodim, S-methyl sulfoxide with an expiration date of 08/19/2017. Additional analytical reference standards are not required.

5.2 Storage Stability

References:
MRID 49958401
MRID 49958402
MRID 49958403

Table 5.2.1 is a summary of the maximum storage intervals for samples between harvest and extraction. Samples were analyzed within 26 days (okra), 6 days (almond nutmeat and hulls), and 28 days (pecans) of extraction.

Table 5.2.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Okra	≤-1	1558-1694 days (51.2-55.7 months)	Residues of clethodim metabolites CSO and 5-OH CSO2 are stable for up to 56.1 months in/on okra, up to 21.8 and 22.1 months in/on almond nutmeat and hulls, respectively, and up to 19.7 months in/on pecan nutmeat.
Almond nutmeat	≤-1	653-718 days (21.5-23.6 months)	
Almond hulls	≤-1	692-726 days (22.7-23.9 months)	
Pecans	≤-1	233-607 days (7.7-19.9 months)	

[1] Interval from harvest to extraction. Samples were analyzed on the day of extraction.

The submitted storage stability studies show that residues of clethodim metabolites CO and 5-OH CSO2 are stable in okra for 56.1 months, almond nutmeat for 21.8, almond hulls for 22.1 months, and pecans for 19.9 months. Samples from the submitted field trials were stored for up to 55.7 months for okra, 23.6 months for almond nutmeat, 23.9 months in almond hulls, and 19.9 months for pecans between harvest and analysis. The submitted storage stability data are adequate to support the storage intervals of the crop field trial data for clethodim in/on okra, almond, and pecan.

5.3 Residue Data

5.3.1 Crop Field Trials

Okra:
Reference:
MRID 49958401

IR-4 has submitted field trial data for clethodim in/on okra from six field trials conducted in the United States during the 2010 growing season. Trials were conducted in North American Free Trade Agreement (NAFTA) Growing Zones 2 (GA, NC, and SC; 3 trials), 3 (FL; 1 trial), 4 (AR; 1 trial), and 6 (TX; 1 trial). The above trial count reflects one pair of trials conducted at the same location that HED has determined to be replicate trials.

Each trial consisted of one untreated plot and one treated plot reflecting four broadcast foliar applications of a 0.97 lb ai/gal EC formulation of clethodim at 0.118-0.129 lb ai/A/application, with 13- to 15-day RTIs, for total seasonal rates of 0.50-0.51 lb ai/A. One trial (FL) received five foliar applications for a total seasonal rate of 0.61 lb ai/A because the okra was not ready for commercial harvest following four applications. Applications were made using ground equipment in spray volumes of 20-38 gal/A. An adjuvant (NIS) was added to the spray mixture for each application. Duplicate samples of okra were harvested at a PHI of 3 days. At one trial (NC), additional samples were collected at PHIs of 0, 8, 10, and 13 days to assess residue decline.

Field trial locations by NAFTA growing zone are summarized in Table 5.3.1.1.

Table 5.3.1.1. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Okra	Sub.		3	1	1		1[2]							6
	Req.[1]		1	1	1		2							5

[1] As per Table 5 of 860.1500 for okra.
[2] Two trials conducted in Zone 6 were determined to be replicates.

Following four broadcast foliar applications of an EC formulation of clethodim at a total seasonal rate of 0.50-0.51 lb ai/A, individual (and per-trial average) residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 ppm) and 0.115-0.478 (0.139-0.470) ppm, respectively, in/on okra harvested at a 3-day PHI; combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) were <0.211-<0.574 (<0.235-<0.566) ppm. Residues were higher in/on okra harvested at a 3-day PHI from the one trial that received five applications at a total rate of 0.61 lb ai/A: <0.096 ppm for DME and 0.429-0.582 (0.506) ppm for DME-OH, for combined residues of <0.525-<0.678 (<0.602) ppm.

In the residue decline trial, residues of DME-OH increased from the 0-day PHI to the 3-day PHI, and decreased thereafter. Residues determined as DME were below the LOQ in/on all samples from the decline trial.

The okra field trial data are acceptable. The data were entered in to the Organization for Economic Co-operation and Development (OECD) tolerance calculator. The OECD tolerance calculator recommends a tolerance level of 1.5 ppm for residues of clethodim in/on okra. The

okra residue data are summarized in Table 5.3.1.2.

Table 5.3.1.2. Summary of Residues from Okra Field Trials with Clethodim.

Crop Matrix	Total Application Rate (lb ai/A)	PHI (days)	Analyte	n[1]	Residues (ppm clethodim equivalents)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Okra	0.50-0.51	3	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH	5	0.115	0.478	0.139	0.470	0.294	0.318	0.126
			Combined	5	<0.211	<0.574	<0.235	<0.566	0.390	0.414	0.126
	0.61	3	DME	1	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH	1	0.429	0.582	0.506	0.506	0.506	0.506	N/A
			Combined	1	<0.525	<0.678	<0.602	<0.602	0.602	0.602	N/A

[1] n = number of field trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial; HAFT = highest average field trial; SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ are assumed to be at the LOQ (0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents). N/A = not applicable.

Almond:

Reference:
MRID 49958402

IR-4 has submitted field trial data for clethodim in/on almonds from five field trials conducted in the United States during the 2013 growing season. Trials were conducted in NAFTA Growing Zone 10 (CA).

Field trial locations by NAFTA growing zone are summarized in Table 5.3.1.3.

Table 5.3.1.3. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Almond	Sub.										5			5
	Req.[1]										5			5

[1] As per Table 5 of 860.1500 for almond.

Each trial consisted of one untreated plot and one treated plot reflecting four soil banded applications of a 0.97 lb ai/gal EC formulation of clethodim at 0.245-0.264 lb ai/A/application, with 13- to 15- day RTIs, for total seasonal rates of 1.01-1.03 lb ai/A. Applications were made using ground equipment in spray volumes of 13-38 gal/A. An adjuvant (NIS) was added to the spray mixture for each application. Duplicate samples of almond nutmeat and hulls were harvested at a PHI of 14-15 days. Residue decline was not investigated.

Following four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 1.01-1.03 lb ai/A, residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 and <0.088 ppm, respectively) in/on almond nutmeat and hulls harvested at a 14- to 15-day PHI, for combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) of <0.184 ppm.

The almond field trial data are acceptable. The residue data clethodim in/on almonds were not entered in to the OECD tolerance calculator as all residue levels were below the LOQ. The almond residue data are summarized in Table 5.3.1.4.

Table 5.3.1.4. Summary of Residues from Almond Field Trials with Clethodim.

Crop Matrix	Total Application Rate (lb ai/A)	PHI (days)	Analyte	n[1]	Residues (ppm clethodim equivalents)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Almond nutmeat	1.01-1.03	14-15	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH		<0.088	<0.088	<0.088	<0.088	0.088	0.088	N/A
			Combined		<0.184	<0.184	<0.184	<0.184	0.184	0.184	N/A
Almond hulls	1.01-1.03	14-15	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH		<0.088	<0.088	<0.088	<0.088	0.088	0.088	N/A
			Combined		<0.184	<0.184	<0.184	<0.184	0.184	0.184	N/A

[1] n = number of field trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial; HAFT = highest average field trial; SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ were assumed to be at the LOQ (0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents). N/A = not applicable.

Pecan:

Reference:
MRID 49958403

IR-4 has submitted field trial data for clethodim on pecans from five field trials conducted in the United States during the 2013-2014 growing seasons. Trials were conducted in NAFTA Growing Zones 2 (NC; 2 trials), 4 (AR; 1 trial), 6 (TX; 1 trial), and 8 (NM; 1 trial).

Field trial locations by NAFTA growing zone are summarized in Table 5.3.1.5.

Table 5.3.1.5. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Pecan	Sub.		2		1		1		1					5
	Req.[1]		2		1		1		1					5

[1] As per Table 5 of 860.1500 for pecan.

Each trial consisted of one untreated plot and one treated plot reflecting four soil banded applications of a 0.97 lb ai/gal EC formulation of clethodim at 0.242-0.254 lb ai/A/application, with 13- to 16- day RTIs, for total seasonal rates of 0.99-1.00 lb ai/A. Applications were made using ground equipment in spray volumes of 20-38 gal/A. An adjuvant (NIS) was added to the spray mixture for each application. Duplicate samples of pecan nutmeat were harvested at a PHI of 14-16 days. Residue decline was not investigated.

Following four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 0.99-1.00 lb ai/A, residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 and <0.088 ppm, respectively) in/on pecan nutmeat harvested at a 14- to 16-day PHI, for combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) of <0.184 ppm.

The pecan field trial data are acceptable. The residue data clethodim in/on pecans were not entered in to the OECD tolerance calculator as all residue levels were below the LOQ. The almond residue data are summarized in Table 5.3.1.6.

Table 5.3.1.6. Summary of Residues from Pecan Field Trials with Clethodim.

Crop Matrix	Total Application Rate (lb ai/A)	PHI (days)	Analyte	n[1]	Residues (ppm clethodim equivalents)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Pecan nutmeat	0.99-1.00	14-16	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH		<0.088	<0.088	<0.088	<0.088	0.088	0.088	N/A
			Combined		<0.184	<0.184	<0.184	<0.184	0.184	0.184	N/A

[1] n = number of field trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial; HAFT = highest average field trial; SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ were assumed to be at the LOQ (0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents). N/A = not applicable.

5.3.2 Magnitude of the Residue - Rotational Crops

Reference:
Memo, 04/13/2016, M. Negussie, D431225

Data concerning the magnitude of residue in rotational crops are not required. The magnitude and nature of the residue in rotational crops is adequately understood based on confined rotational crop studies with rotated carrots, lettuce, and wheat. The results indicate that there is no need for field rotational crop trials and that a 1-month plantback interval will be appropriate. The submitted labels include the following restriction: do not plant rotational crops until 30 days after application of Select 2 EC Herbicide and V-10137 1 EC Herbicide.

5.3.3 Processed Food/Feed

Processed food/feed commodities are not of concern for tree nuts and okra.

5.3.4 Meat, Milk, Poultry, and Eggs

References: Memo, 07/09/2007, J. Stokes, D333329

Livestock tolerances for residues of clethodim and its metabolites in/on livestock commodities are currently established. Almond hulls are a livestock feedstuff. The potential for secondary transfer of clethodim residues of concern in meat and milk exists from the proposed use on almond hulls as well as from registered uses on crops with feedstuffs. Please note: Almonds hulls are a feedstuff for dairy cattle only at up to 10% of the diet. Using the Table 1 Feedstuffs (October 2006), the burdens of clethodim to beef and dairy cattle, poultry, and swine were previously determined based on reasonably balanced diets. The dietary burdens are: beef cattle – 3.95 ppm; dairy cattle- 4.11 ppm; poultry – 3.14 ppm; and swine – 2.16 ppm. The addition of almond hulls to the diet of dairy cattle does not significantly increase the dietary burden. Thus, HED concludes that the current petition does not alter the previous decisions concerning the magnitude of the residue in/on livestock.

5.4 Food Residue Profile

Based on the proposed/registered application scenarios, clethodim may be found in drinking water and crop commodities.

6.0 Tolerance Derivation

Okra: The okra field trial data are acceptable. The data from the field trials were entered in to the OECD tolerance calculator. The OECD tolerance calculator recommends a tolerance level of 1.5 ppm for residues of clethodim and its metabolites in/on okra.

Fruiting Vegetables, Group 8-10, except okra: The tolerance level for residues of clethodim and its metabolites in/on the fruiting vegetables, group 8-10, except okra, are based on the established tolerance for residues of clethodim and its metabolites in/on fruiting vegetables, group 8-10 at 1.0 ppm.

Tree Nuts, Group 14: Residue data for clethodim and its metabolites in/on almonds and pecans were submitted. The data show that residues of clethodim and its metabolites are below the LOQ (<0.20 ppm) in/on almond nutmeat and hulls, and pecan nutmeat.

Stalk and Stem Vegetable, Subgroup 22A: The tolerance level for residues of clethodim and its metabolites in/on the stalk and stem subgroup 22A are based upon the established tolerance for residues of clethodim and its metabolites in/on asparagus at 1.7 ppm. Asparagus is the representative commodity for the stalk and stem vegetable, subgroup 22A.

Brassica, Head and Stem, Group 5-16: The tolerance level for residues of clethodim and its metabolites in/on the *Brassica*, head and stem, group 5-16 are based on the established tolerance for residues of clethodim and its metabolites in/on *Brassica*, head and stem, subgroup 5A at 3.0 ppm.

Brassica, Leafy Greens, Subgroup 4-16B: The tolerance level for residues of clethodim and its metabolites in/on the *Brassica*, leafy greens, group 5-16 are based on the established tolerance for residues of clethodim and its metabolites in/on *Brassica*, leafy greens, subgroup 5B at 3.0 ppm.

Leaf Petiole Vegetable, Subgroup 22B: The tolerance level for residues of clethodim and its metabolites in/on the leaf petiole, subgroup 22B are based on the established tolerance for residues of clethodim and its metabolites in/on leaf petioles, subgroup 4A at 2.0 ppm.

Leafy Greens, Subgroup 4-16A: The tolerance level for residues of clethodim and its metabolites in/on the leafy greens, subgroup 4-16A is based on the established tolerance for residues of clethodim and its metabolites in/on leaf greens, subgroup 4A at 2.0 ppm.

Green Onion, subgroup 3-07B: The tolerance level for residues of clethodim and its metabolites in/on the green onion, subgroup 3-07B is based on the established tolerance for residues of clethodim and its metabolites in/on green onion at 2.0 ppm. Green onions are the representative commodity for the green onion, subgroup 3-07B.

Table 6.0.1 is a summary of the proposed and HED recommended tolerances.

Table 6.0.1. Tolerance Summary for Clethodim.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Nuts, Tree, Group 14-12	0.2	0.20	
Almond, Hulls	0.2	0.20	
Okra	1.5	1.5	
Vegetable, Fruiting, Group 8-10 except okra	1.0		
Stalk and Stem Vegetable, Subgroup 22A	1.7	1.7	
Vegetable, *Brassica*, Head and Stem, Group 5-16	3.0		
Brassica, Leafy Greens, Subgroup 4-16B	3.0		
Leaf Petiole Vegetable, Subgroup 22B	0.60		

Leafy Greens, Subgroup 4-16A	2.0		
Onion, green, Subgroup 3-07B	2.0		

Upon establishment of the requested tolerances, remove established tolerances for residues of the herbicide clethodim, including its metabolites and degrades in or on the commodities listed in the following table.

Raw Agricultural Commodities/Crop Group	**Established Tolerance (ppm)**
Asparagus	1.7
Brassica, Head and Stem, Subgroup 5A	3.0
Brassica, Leafy Greens, Subgroup 5B	3.0
Leafy Petioles, Subgroup 4B	0.60
Leafy Greens, Subgroup 5B	2.0
Onion, green	2.0
Turnip Greens	3.0
Vegetable, Fruiting, Group 8-10	1.0

7.0. REFERENCES

Memo, 04/13/2016, M. Negussie, D431225
MRID 49527101
MRID 49527102
Memo, 1/31/95, J. Morales, PP#4F4340, D203378
Correspondence with G. Verdin, BEAD/ACL, 06/05/2017.
MRID 49958401
MRID 49958402
MRID 49958403

Attachment 1: International Residue Limits.
Attachment 2: Chemical Structures
Attachment 3: Proposed Metabolic Profile of Clethodim in Carrot
Attachment 4: Proposed Metabolic Profile of Clethodim in Spinach
Attachment 5: OECD MRL Calculation Procedure Inputs/Outputs

Attachment 1: International Residue Limits.

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[2]	Codex
Plant: Residues of clethodim and its metabolites containing the 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulphoxides and sulphones, expressed as clethodim.				None

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex
Nuts, Tree, Group 14-12	0.20			
Almond, Hulls	0.20			
Okra	1.5			
Vegetable, Fruiting, Group 8-10 except okra	1.0			
Stalk and Stem Vegetable, Subgroup 22A	1.7			
Vegetable, *Brassica*, Head and Stem, Group 5-16	3.0			
Brassica, Leafy Greens, Subgroup 4-16B	3.0			
Leaf Petiole Vegetable, Subgroup 22B	0.60			
Leafy Greens, Subgroup 4-16A	2.0			
Onion, green, Subgroup 3-07B	2.0			
Completed: M. Negussie; 04/07/2016				

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.
[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Attachment 2: Chemical Structures.

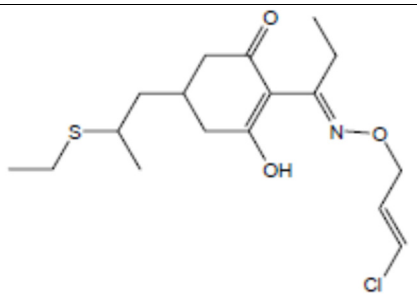
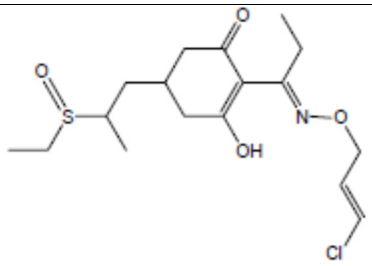
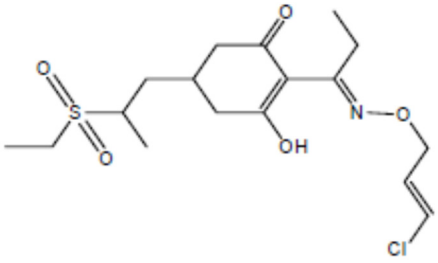
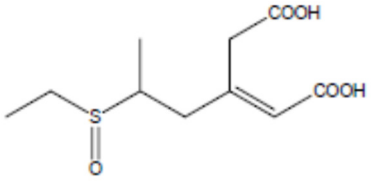
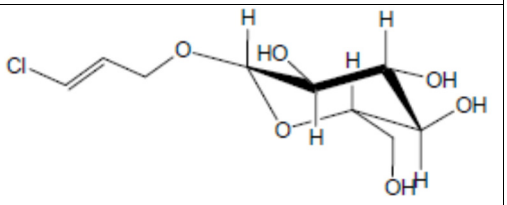
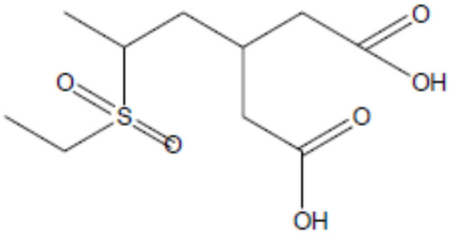
Table A2. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Clethodim	(*E,E*)-(±)-2-[1[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one	
Clethodim sulfoxide; M29 and M37	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfinyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Clethodim sulfone; M33 and M41	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfonyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid; M15R (tentative identification)	Not provided	
3-Chloroallyl alcohol glucoside; M15A (tentative identification)	Not provided	
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid; M17R and M16R	Not provided	

Table A2. Identification of Compounds from Metabolism Study (both proposed and found).

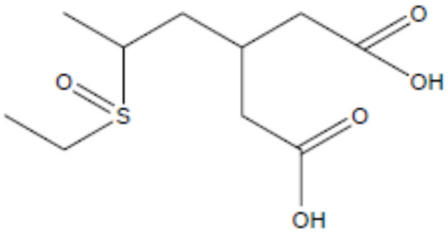
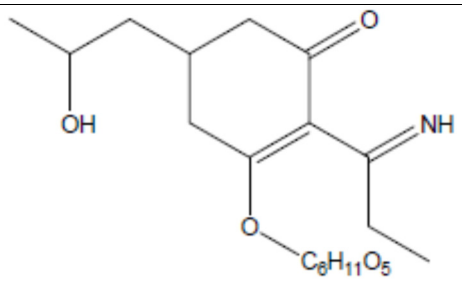
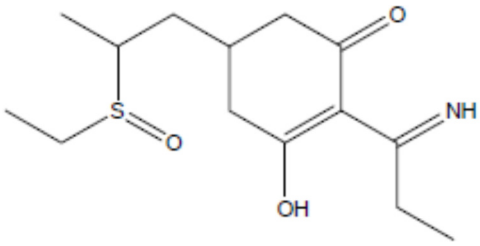
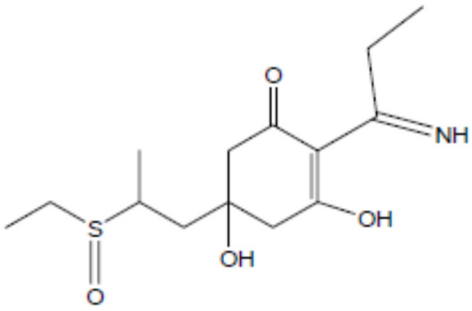
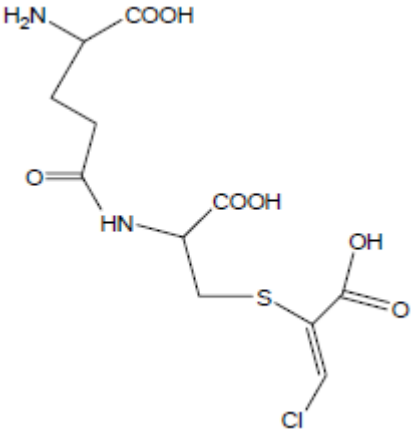
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid; M18R	Not provided	
Imine glucose conjugate; M19R (tentative identification)	Not provided	
Clethodim imine sulfoxide and hydroxy imine sulfoxide (M22R) (tentative identification)	Not provided	 and 
2-(Glutamyl-cysteinyl-3-chloroacrylic acid; M22A (tentative identification)	Not provided	

Table A2. Identification of Compounds from Metabolism Study (both proposed and found).

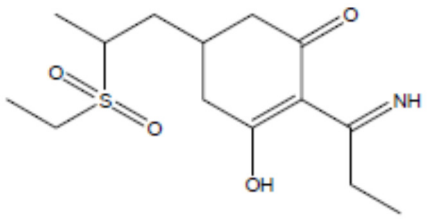
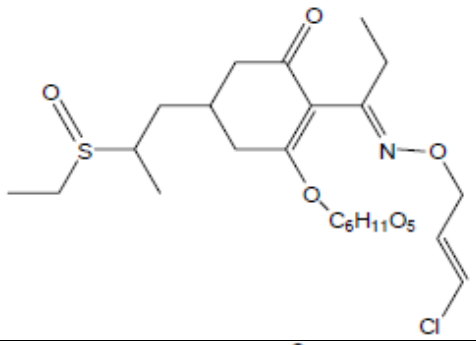
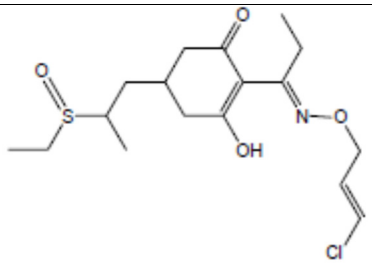
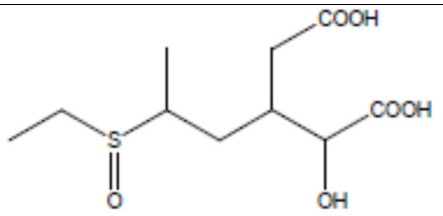
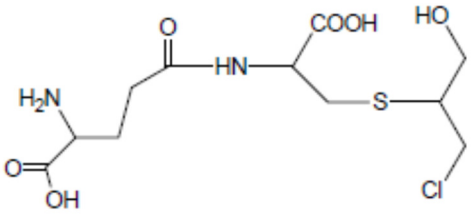
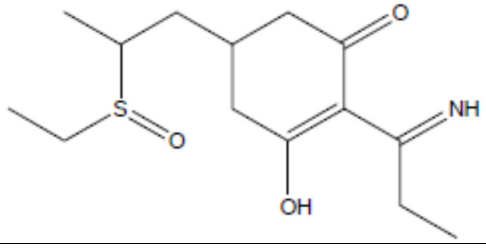
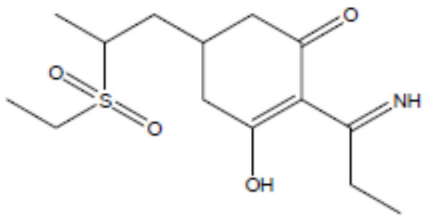
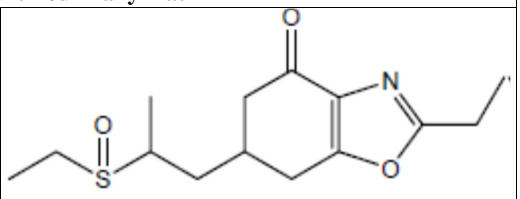
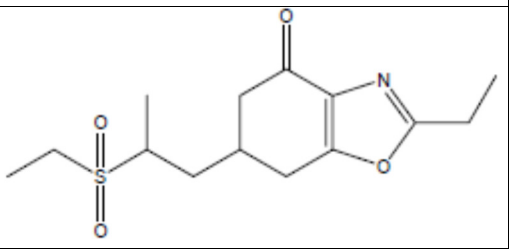
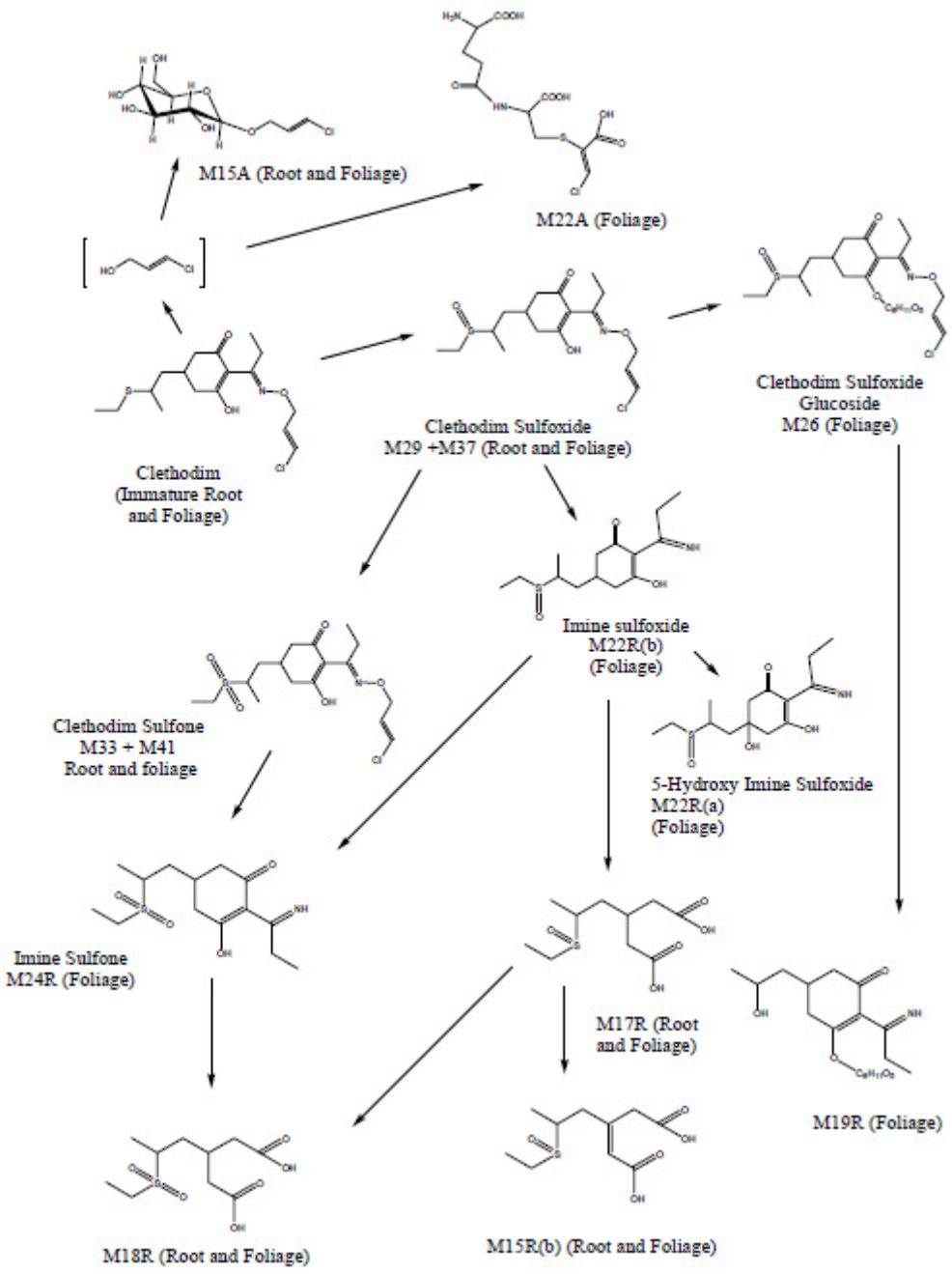
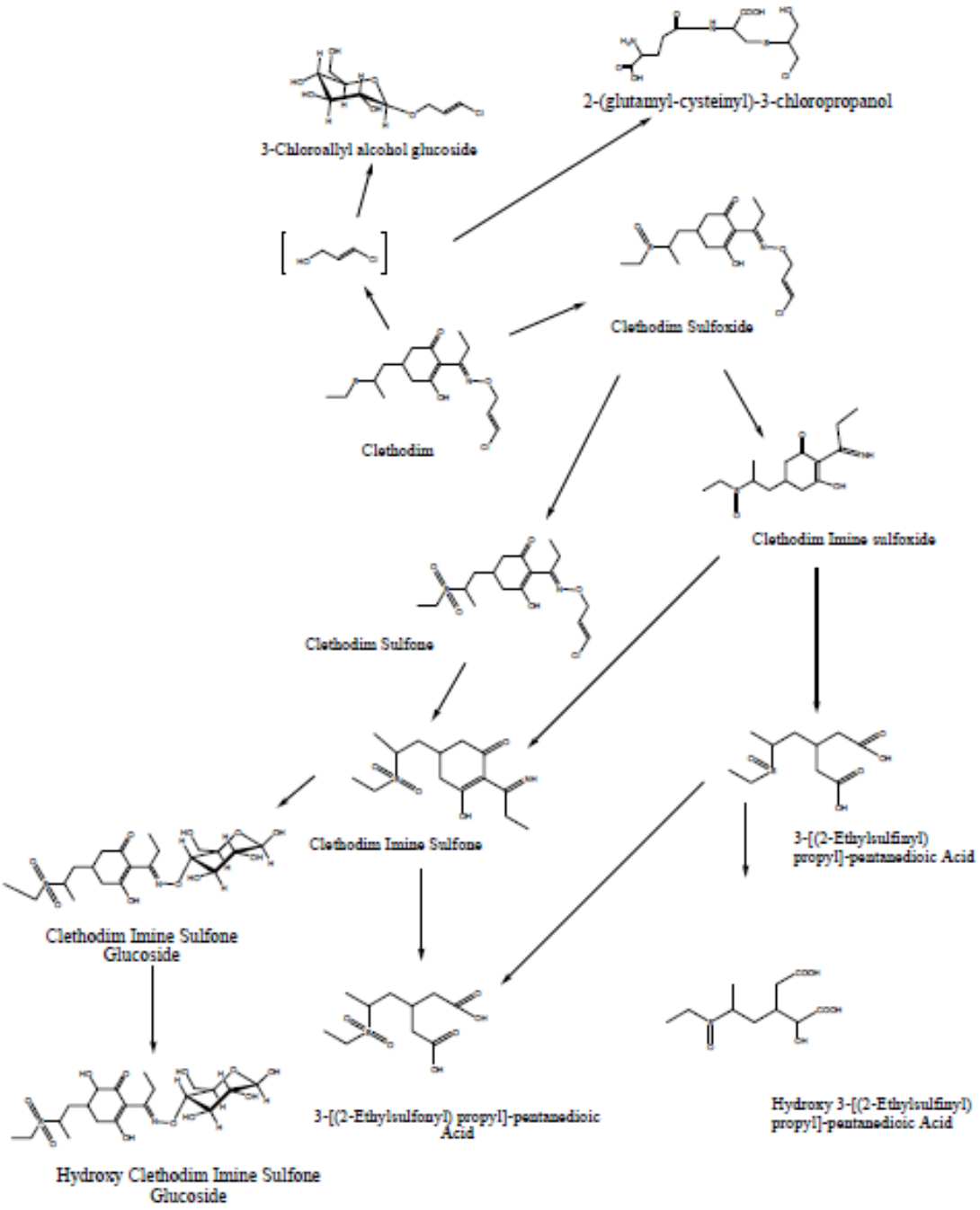
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Clethodim imine sulfone (M24R) (tentative identification)	Not provided	
Clethodim sulfoxide glucoside (M26) (tentative identification)	Not provided	
Clethodim sulfoxide; M28 and M37	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfinyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Hydroxy 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid; M14R (tentative identification)	Not provided	
2-(Glutamyl-cysteinyl-3-chloropropanol; M19A (tentative identification)	Not provided	
Clethodim imine sulfoxide (M21R) (tentative identification)	Not provided	

Table A2. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Clethodim imine sulfone (M23R) (tentative identification)	Not provided	
Additional reference standard compounds used in the study but not identified in any matrix		
Clethodim oxazole sulfoxide	Not provided	
Clethodim oxazole sulfone	Not provided	

Attachment 3: Proposed Metabolic Profile of Clethodim in Carrot.



Attachment 4: Proposed Metabolic Profile of Clethodim in Spinach.



Attachment 5: OECD MRL Calculation Procedure Inputs/Outputs

Okra:

Clethodim
Okra
US
0.50-0.51 lb ai/A

Residues (mg/kg)	
0.495	
0.566	
0.235	
0.602	
0.386	
0.390	

Clethodim
Okra
US
0.50-0.51 lb ai/A

Total number of data (n)	6
Percentage of censored data	0%
Number of non-censored data	6
Lowest residue (LR)	0.235
Highest residue (HR)	0.602
Median residue (STMR)	0.443
Mean	0.446
Standard deviation (SD)	0.136
Correction factor for censoring (CF)	1.000
Proposed MRL estimate	
Unrounded	1.337
Rounded to the next MRL class	**1.5**

High uncertainty of MRL estimate due to small dataset.

B.7.1 Metabolism, Distribution, and Expression of Residues in Plants (Annex IIA 6.2; Annex IIIA, 8.2)

B.7.1.1 Carrot

Date:	**03/05/2018**
Document ID:	MRID No. 49527101
Report:	Dohn, D., Sugiyama, K., and Woodbury, S. (2010) The Metabolism of [^{14}C]Clethodim (2 Radiolabels) in Carrot (*Daucus carota*). Laboratory Project Nos. 1808W and 1808W-1. Unpublished study prepared by Arysta LifeScience North America, LLC. 304 p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1300 Nature of the Residue - Plants, Livestock (August 1996) PMRA Regulatory Directive Dir98-02 – Residue Chemistry Guidelines, Section 2 -Nature of the Residue - Plants, Livestock OECD Guideline 501 Metabolism in Crops (January 2007)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP# 349748.
Evaluator:	William D. Wassell, Chemist RAB3/HED

Note: This Data Evaluation Record (DER) was originally prepared under contract by Versar, Inc. (6850 Versar Center, Springfield, VA 22151; submitted 7/14/15). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

Arysta Life Science EAME has submitted a study investigating the metabolism of ring-labeled [4,6-cyclohexen-^{14}C]clethodim (ring label; specific activity 1.51 MBq/mg (Megabecquerel/milligram) and [allyl-2-^{14}C]clethodim (allyl label; specific activity 1.68 MBq/mg) following foliar application to carrot. The radiolabeled test substances were formulated as suspension concentrate (SC) formulations and applied to carrots in outdoor plots as a single foliar broadcast application at 0.557-0.569 lb ai/A (624-638 g ai/ha). Carrots were harvested at preharvest intervals (PHIs) of 21 and 56 days and separated into roots and tops. The in-life phase of the study was conducted by Excel Research Services (Fresno, CA), and the analytical phase of the study was conducted by PTRL West, Inc. (Hercules CA).

Total radioactive residues (TRR) were determined by combustion/LSC (Liquid Scintillation Counting) and by summing extractable and nonextractable radioactivity. The summed TRR in ring-label carrot matrices were: 5.714 and 0.815 ppm in immature tops and roots and 0.842 and 0.158 ppm in mature tops and roots. The summed TRR in allyl-label matrices were: 3.888 and 0.738 ppm in immature tops and roots and 0.752 and 0.131 ppm in mature tops and roots. Surface rinses of the roots with water removed 0.066-0.093 ppm from immature roots and 0.003-0.007 ppm from mature roots.

Extraction with acetonitrile (ACN)/water released the majority of the radioactivity from immature and mature carrot matrices: 83.4-87.1% TRR for ring-label carrots and 70.9-77.1% TRR for allyl-label carrots. Sequential extraction with ACN, ACN/0.2 N HCl (hydrochloric acid), and ACN/0.2 N NH_4OH (ammonium hydroxide) released minor amounts of radioactivity (≤3.8% TRR for any solvent in any matrix) as did sequential hydrolysis of the remaining nonextractable residues for all matrices except ring-label mature root with 0.05 M EDTA (ethylenediaminetetraecetic acid) and 1 N HCl (≤4.9% TRR). Final hydrolysis with 24% KOH (potasium hydroxide) (ambient temperature, overnight) released 3.3-7.5% TRR from ring-label matrices and 7.2-10.8% TRR from allyl-label matrices. Attempts to further investigate this hydrolysate by partitioning with DCM (dichloromethane) under acidic and basic conditions were unsuccessful. The nonextractable residues remaining following extraction and hydrolysis procedures were: 0.7% TRR (0.038 ppm) and 1.6% TRR (0.013 ppm) in immature ring-label tops and roots; 1.0% TRR (0.008 ppm) and 8.2% TRR (0.013 ppm) in mature ring-label tops and roots; 2.1% TRR (0.080 ppm) and 2.7% TRR (0.020 ppm) in immature allyl-label tops and roots; and 2.3% TRR (0.017 ppm) and 2.3% TRR (0.003 ppm) in mature allyl-label tops and roots. These procedures adequately extracted the majority of residues from all carrot matrices. Extraction results were normalized; therefore, accountabilities were ~100%.

Residues were quantified and parent and the clethodim sulfoxide and sulfone metabolites were identified in the ACN/water extracts of carrot matrices by high performance liquid chromatography with ultraviolet (UV) detection (HPLC/UV). Identification of clethodim sulfoxide and clethodim sulfone was confirmed by thin layer co-chromatography (TLC). Remaining metabolites were identified or tentatively identified by high performance liquid chromatography with tandem mass spectrometry detection (LC/MS/MS) in conjunction with HPLC co-chromatography for certain metabolites. Samples of immature and mature carrot tops and roots were stored frozen (~-20 °C) and were initially analyzed within 40-42 days (1.3-1.4 months) of harvest. Based on dated chromatograms, LC/MS/MS analyses of immature foliage extracts were completed within 228 days (7.5 months) of harvest. Repeat HPLC analysis of the ACN/water extracts of immature tops conducted within 216 days (7.1 months) of harvest indicated that the metabolite profile was generally stable during frozen storage. No additional storage stability data are required to support the study.

Clethodim was a minor residue component identified in the ACN/water extracts of immature tops and roots only (both labels) at <0.1-0.2% TRR. Clethodim sulfoxide was the major identified residue component in all matrices (both labels), accounting for 11.3-11.8% TRR (0.095-0.663 ppm) and 16.2-18.4% TRR (0.029-0.132 ppm) in ring-label tops and roots, respectively, and for 19.4-21.7% TRR (0.164-0.757 ppm) and 22.1-24.4% TRR (0.032-0.163 ppm) in allyl-label tops and roots, respectively. Clethodim sulfone was also identified at slightly higher levels in roots than in tops for both labels: at 3.2-4.8% and 6.3-7.0% TRR in ring-label tops and roots, and at 6.0-6.1% and 7.7-9.9% TRR in allyl-label tops and roots. In ring-label carrots, five additional metabolites were identified or tentatively identified as major residue components in one or more matrices: (1) dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R) in all matrices at 3.6-12.0% TRR (0.019-0.594 ppm); (2) 3-[(2-ethylsulfinyl)propyl]-pentanedioic acid (M17R) in all matrices at 8.9-13.9% TRR (0.022-0.519 ppm); (3) 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid (M18R) in all matrices at 7.3-12.7% TRR (0.020-0.410

ppm); (4) an imine glucose conjugate (M19R) in immature and mature tops at 11.2-14.1% TRR (0.119-0.633 ppm); and (5) an imine sulfoxide and hydroxy imine sulfoxide metabolite pair (M22R) in immature tops only at 12.6% TRR (0.710 ppm). Two additional metabolites were tentatively identified in immature and mature tops only: imine sulfone (M24R) at 6.5-7.4% TRR (0.062-0.369 ppm) and clethodim sulfoxide glucoside (M26) at 6.4-9.3% TRR (0.078-0.360 ppm). Clethodim sulfoxide glucoside (M26) was the only metabolite, other than clethodim sulfoxide and sulfone, that was also identified in allyl-label matrices, where it accounted for 9.9-14.6% TRR (0.111-0.385 ppm) in immature and mature tops. Remaining metabolites identified in allyl-label matrices were minor components: a 3-chloroallyl glucoside (M15A) at 3.1-6.5% TRR in all matrices; and 2-(glutamyl-cysteinyl)-3-chloracrylic acid (M22A) at 7.3% TRR in immature and mature tops only. A highly polar, acidic metabolite (M3A) was a major residue component (11.0-15.3% TRR, 0.020-0.081 ppm) in allyl-label roots; less radioactivity eluted with this fraction in ring-label carrot and was not investigated. No structure was proposed for M3A. Remaining discrete unknowns accounted for 2.8-10.1% TRR in ring-label carrot matrices (0.016-0.157 ppm; two unknowns, none >6.3% TRR) and for 12.9-17.2% TRR (0.130-0.501 ppm; four unknowns, none >7.0% TRR) in allyl-label tops and 4.3-8.4% TRR (0.011-0.032 ppm; two unknowns, none >6.1% TRR) in allyl-label roots. As noted above, remaining extraction/hydrolysis procedures released minor amounts of radioactivity except for hydrolysis with 24% KOH.

Based on the results of the carrot metabolism study, the petitioner concluded that clethodim was metabolized extensively in carrot, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring.

I. MATERIALS AND METHODS

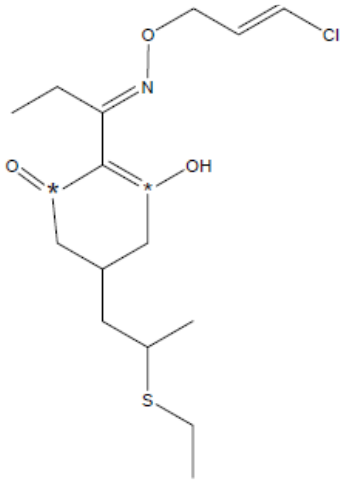
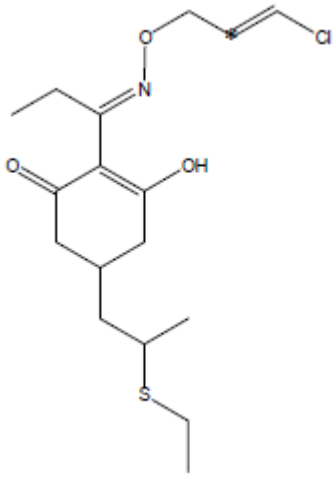
A. MATERIALS

1. Test Material

The radiolabeled test substances in ethanol were isotopically diluted with nonlabeled clethodim in ethanol. The ethanol was removed by evaporation under nitrogen, and the test substances were formulated as 2.0 lb ai/gal (240 g ai/L) SC formulations by mixing with formulation blank and water.

Table B.7.1.1-1. Clethodim Nomenclature.

Common name	Clethodim
Identity	(*E,E*)-(±)-2-[1[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one
CAS no.	99129-21-2
Company experimental name	Not applicable
Other synonyms (if applicable)	Not applicable
Lot/Batch #	Ring label: [4,6-cyclohexen-^{14}C]clethodim: 448-151-0525
	Allyl label: [allyl-2-^{14}C]clethodim: 448-152-0597
Radiochemical purity	Ring label: 97.2%
	Allyl label: 96.8%
Specific activity as received	Ring label: 52.5 mCi/mmol (3.25 x 10^8 dpm/mg)

Table B.7.1.1-1. Clethodim Nomenclature.	
	Allyl label: 59.7 mCi/mmol (3.68 x 10^8 dpm/mg)
Specific activity of dose	Ring label: 1.51 MBq/mg (9.08 x 10^7 dpm/mg)
	Allyl label: 1.68 MBq/mg (1.01 x 10^8 dpm/mg)
Position of radiolabels Ring label:  Allyl label: 	

2. Test Crop

The in-life phase of the study was conducted by Excel Research Services near Madera, CA, and the analytical phase of the study was conducted by PTRL West (Hercules, CA). Carrots were grown from seed in outdoor plots consisting of above-ground wooden boxes (1 m^2) filled with sandy loam soil to a depth of 23 cm. Weather conditions were reported to be normal during the experimental phase of the study. Carrots were maintained according to typical agronomic practices and were watered by hand as needed. Weather and irrigation data were provided. Plants were fertilized once; no pesticides were used during the study.

Table B.7.1.1-2. Crop Information.				
Crop/Crop Group	Variety	Growth Stage at Application	Growth Stage at Harvest	Harvested Commodities
Carrot/ Root and tuber vegetable, group 1; and Leaves of root and tuber vegetable, group 2	Half Long 126	BBCH 15-18	Immature: BBCH 45 Mature: BBCH 48-49	Tops and roots

3. Soil Type

Table B.7.1.1-3. Soil Physicochemical Properties.							
Soil Type	pH	OM %	Sand %	Silt %	Clay %	Moisture Holding Capacity (at 1/3 bar)	CEC (meg/100 g)
Sandy loam	7.4	1.3	75	15	10	12.0	9.7

OM = organic matter, CEC = cation-exchange capacity.

B. STUDY DESIGN

Experimental Conditions

The radiolabeled test substances were formulated as SC formulations and applied to carrots in outdoor plots as a single foliar broadcast application at 0.557-0.569 lb ai/A (624-638 g ai/ha) made 42 days after planting.

Table B.7.1.1-4. Use Pattern Information.	
Chemical name	[4,6-cyclohexen-14C]clethodim (ring label) and [allyl-2-14C]clethodim (allyl label)
Application method	The formulated test substances were applied as a single foliar broadcast application using hand-operated pump spray nozzles
Application rate	Ring label: 0.569 lb ai/A (638 g ai/ha) Allyl label: 0.557 lb ai/A (624 g ai/ha)
Number of applications	1
Timing of applications	42 days after planting
PHI	Immature: 21 days Mature: 56 days

Sampling

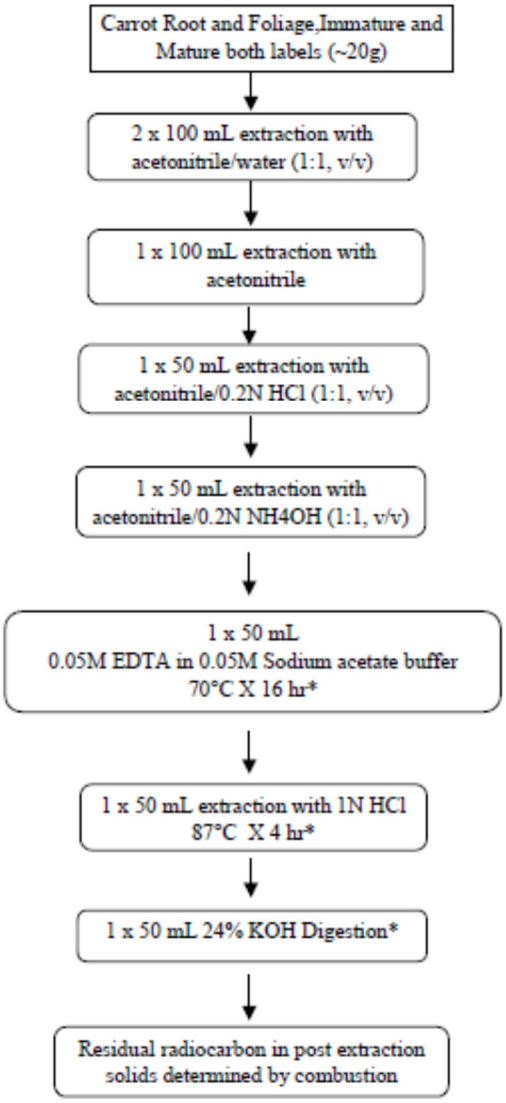
Immature and mature carrots were harvested at PHIs of 21 and 56 days, respectively. Tops were collected by cutting from the plants using pruning shears. Roots were then pulled from the soil and rinsed with water, and the water rinses were also collected. All samples were placed in frozen storage (temperature not specified) until shipment via ACDS freezer truck or on dry ice via FedEx to the analytical laboratory, PTRL West, Inc. (Hercules CA). At PTRL West, samples were stored frozen (~-20 °C) prior to analysis. Samples were prepared for extraction by homogenizing in the presence of dry ice.

Extraction and Analysis

Samples of carrot roots and tops were extracted sequentially with ACN:water (1:1, v:v; 2x), ACN, and ACN:0.2 N HCl (1:1, v:v), and were centrifuged after each step. The initial ACN/water extracts were combined, concentrated by rotary evaporation, and reserved for HPLC analysis. The nonextractable residues of all matrices except ring-label mature root were subjected to further sequential extraction/hydrolysis with: (1) ACN:0.2 N NH_4OH (1:1, v:v, at ambient temperature for 45 minutes); (2) 0.05 M EDTA (in 0.05 M sodium acetate buffer, pH 4.90, at 70 °C overnight); (3) 1 N HCl (at 87 °C for 4 hours); and (4) 24% KOH (at ambient temperature, overnight). Extracts and hydrolysates were collected by centrifugation. The 24% KOH hydrolysates were vacuum filtered for further clarification, and the filter paper and its contents were reserved for combustion/LSC. The 24% KOH hydrolysates were subsequently partitioned with dichloromethane (DCM) under basic and acidic conditions (pH 14 and pH 2).

A flowchart of the extraction procedures is presented (copied without alteration from MRID 49527101) in Figure B.7.1.1-1.

FIGURE B.7.1.1-1. Extraction and Fractionation of Carrot Samples.



* These extractions were not performed on the mature carrot roots from the [ring-^{14}C]clethodim application.

Extractions performed at ambient temperature unless specified otherwise.

Identification and Characterization

The ACN/water extracts of carrot roots and tops were subjected to reverse-phase HPLC/UV (Method 1) for quantification and identification of residues using a system equipped with a Capcell C-18 column and a UV detector (230 nm) and using a gradient mobile phase of water and ACN, each containing 0.1% formic acid. Radioactive components were detected and quantified by fraction collection coupled with LSC or using a flow-through radiodetector. In addition, metabolites were isolated and purified from the combined ACN/water extracts of immature foliage using HPLC with fraction collection on the following systems: Method 2 using

an Inertsil Phenyl column and the same mobile phase with a different gradient; Method 3 using an Inertsil Phenyl column and a gradient mobile phase of water and methanol, each containing 0.1% formic acid; and Method 4 using the same column and mobile phase as Method 1 with a different gradient. Identification of clethodim sulfoxide and clethodim sulfone was confirmed by normal-phase TLC co-chromatography on silica gel F_{254} plates using a solvent system of chloroform:isopropanol:acetic acid (9:1:1, v:v:v). Radioactivity was detected by phosphorimaging; the nonlabeled standard was visualized under UV light.

The petitioner noted that clethodim and its metabolites containing the oxime ether linkage, clethodim sulfoxide and clethodim sulfone, equilibrated rapidly between their two geometric isomers (*syn* and *anti* forms) on the HPLC column; therefore, these analytes chromatographed as two distinct peaks with intervening (equilibrating molecules eluting between the two major peaks). Clethodim sulfoxide and clethodim sulfone were quantitated as the sum of the two peaks and any radiocarbon eluting between the peaks; however, clethodim was quantitated on the basis of the later eluting isomer only because residues of the earlier eluting isomer were below the LOQ of the study.

Metabolite fractions were isolated and purified from combined ACN/water extracts of ring- and allyl-label immature foliage to aid in identification of residues. The extracts were concentrated by rotary evaporation and partitioned with hexane, and the resulting aqueous phase was reduced under nitrogen for preparative HPLC using Method 1. Fractions were collected at 30-second intervals, and fractions corresponding to the peaks of interest were combined as appropriate. The isolated metabolites were further purified using Methods 2, 3, and/or 4, and the predominant radioactive peaks were subjected to LC/MS/MS using an LCQ Fleet mass spectrometer interfaced with HPLC/UV. For MS/MS analysis the system used ESI or APCI in both the positive and negative scanning modes.

The following metabolites were identified in ring-label carrot by LC/MS/MS analysis. Metabolite M15R was tentatively identified as dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid on the basis of results which indicated that it possessed the ethyl sulfinyl moiety and lacked the oxime ether moiety. Metabolites M17R and M18R were identified as 3-[(2-ethylsulfinyl)propyl]-pentanedioic acid and 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid, respectively, on the basis of LC/MS/MS and HPLC co-chromatography with reference standards that were provided by the sponsor once the LC/MS/MS work had been completed. Glucose conjugate metabolite M19R was tentatively identified based on results characteristic for a glucose conjugate and the absence of the oxime ether moiety, along with an ion transition indicating the loss of glucose minus water. Clethodim hydroxy imine sulfoxide and clethodim imine sulfoxide, the two components comprising metabolite M22, were identified following separation of the metabolite on purification. The two metabolites, along with the imine sulfone metabolite (M24R) were tentatively identified based on comparison of ion pairs in the ESI (-) and ESI (+) modes suggesting imine and hydroxylated imine sulfoxides and an ion transition indicating the loss of ethyl sulfenic acid, as well as by molecular weight comparisons. Finally, clethodim sulfoxide glucoside (M26) was tentatively identified based on comparison of ion pairs in the ESI (-) and ESI (+) modes suggesting a clethodim sulfoxide glucose conjugate and ion transitions indicating the loss of formic acid and of glucose minus water.

LC/MS/MS analysis of allyl-label foliage extracts confirmed the identification of clethodim sulfoxide glucose conjugate (M26) in the allyl-label matrices. Metabolites M15A and M22 A were tentatively identified as 3-chloroallyl alcohol glucoside and 2-glutamyl-cysteinyl-3-chloroacrylic acid (on the basis of molecular weight and results characteristic of the respective conjugates. In addition, Unknown M3A was characterized as a highly polar and acidic compound on the basis of the following: (1) hydrolysis with 1 N HCl and 1 N NaOH (each for 1 hour at reflux); (2) derivatization with diazomethane and 3 N HCl in butanol; (3) additional HPLC analyses using Luna Amino and Luna HILIC columns; (4) and LC/MS/MS analysis using a TSK gel amide column. No structure could be proposed for this metabolite.

The 24% KOH hydrolysates were partitioned with DCM under basic and acidic conditions in an attempt to release additional radioactivity for chromatographic analysis; however, the majority of radioactivity remained in the aqueous phase for all matrices, both labels.

II. RESULTS AND DISCUSSION

A. Total Radioactive Residues

Quantitation

TRR were determined by direct combustion/LSC and by summing extractable and nonextractable radioactivity. TRR in homogenized plant matrices and post-extraction solids (PES) were determined by combustion/LSC; TRR in surface rinses and extracts were determined by direct LSC. Summed TRR were used for all subsequent calculations.

The TRR in carrot samples are summarized in Table B.7.1.1-5.

Table B.7.1.1-5. TRR in Carrot.

Matrix		Residues (ppm [^{14}C]clethodim equivalents)			
		Ring-label		Allyl-label	
		Combustion/LSC	Summed[1]	Combustion/LSC	Summed[1]
Immature:	Tops	6.166	5.714	4.158	3.888
	Root	0.858	0.815	0.742	0.738
	Rinse water (root)	0.093	--	0.066	--
Mature:	Tops	0.826	0.842	0.791	0.752
	Root	0.153	0.158	0.125	0.131
	Rinse water (root)	0.007	--	0.003	--

[1] Calculated by summing extractable and nonextractable radioactivity. These values were used for all further determinations.

B. Extraction, Characterization, and Distribution of Residues

Extraction and characterization of residues in carrot

The distribution of radioactivity in carrot tops and roots is presented in Tables B.7.1.1-6 (ring label) and B.7.1.1-7 (allyl label).

Ring label:

Table B.7.1.1-6. Distribution of the Parent and the Metabolites in Carrot Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.569 lb ai/A (638 g ai/ha).[1]

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =5.714 ppm)		(TRR = 0.815 ppm)		(TRR = 0.842 ppm)		(TRR = 0.158 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	87.1	4.978	84.4	0.688	83.4	0.702	86.7	0.137
Clethodim	<0.1	0.004	0.2	0.002	--	--	--	--
Clethodim sulfoxide (total)[2]	11.8	0.663	16.2	0.132	11.3	0.095	18.4	0.029
Clethodim sulfoxide (M29)	[4.7]	[0.264]	[5.0]	[0.041]	[7.4]	[0.062]	[7.6]	[0.012]
Clethodim sulfoxide (M37)	[7.1]	[0.399]	[11.2]	[0.091]	[3.9]	[0.033]	[10.8]	[0.017]
Clethodim sulfone (total)[2]	3.2	0.180	6.3	0.051	4.8	0.040	7.0	0.011
Clethodim sulfone (M33)	[1.9]	[0.109]	[3.8]	[0.031]	[3.7]	[0.031]	[5.1]	[0.008]
Clethodim sulfone (M41)	[1.3]	[0.071]	[2.5]	[0.020]	[1.1]	[0.009]	[1.9]	[0.003]
Dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R)	10.5	0.594	7.7	0.063	3.6	0.030	12.0	0.019
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M17R)	9.2	0.519	13.1	0.107	8.9	0.075	13.9	0.022
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M18R)	7.3	0.410	8.8	0.072	8.1	0.068	12.7	0.020
Imine glucose conjugate (M19R)	11.2	0.633	--	--	14.1	0.119	--	--
Clethodim Imine sulfoxide and hydroxy imine sulfoxide (M22R)	12.6	0.710	--	--	--	--	--	--
Clethodim imine sulfone (M24R)	6.5	0.369	--	--	7.4	0.062	--	--
Clethodim sulfoxide glucoside (M26)	6.4	0.360	--	--	9.3	0.078	--	--
Unknown M3R	0.4	0.024	2.5	0.020	0.4	0.003	3.8	0.006
Unknown M27	2.4	0.133	3.2	0.026	3.1	0.026	6.3	0.010
CAN	1.0	0.057	2.9	0.024	1.3	0.011	3.8	0.006
ACN/0.2 N HCl	1.2	0.066	1.7	0.014	2.0	0.017	1.3	0.002
ACN/0.2 N NH_4OH	1.9	0.109	2.5	0.020	1.9	0.016		
0.05 M EDTA	1.5	0.085	1.5	0.012	1.3	0.011		
1 N HCl	1.8	0.101	2.0	0.016	1.5	0.013		
24% KOH	4.8	0.276	3.3	0.027	7.5	0.063		
DCM (pH 14)	<0.1	0.001	<0.1	<<0.001	<0.1	<<0.001		
DCM (pH 2)	0.1	0.003	<0.1	<<0.001	0.2	0.001		
Aqueous	3.6	0.203	3.2	0.026	7.3	0.061		
24% KOH filter paper	0.1	0.004	0.1	0.001	0.1	0.001		
Nonextractable	0.7	0.038	1.6	0.013	1.0	0.008	8.2	0.013

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the fraction in question.
[2] Residues of clethodim sulfoxide and clethodim sulfone eluted in two peaks as the result of *syn/anti* inter-conversion of oxime ethers. Total values were calculated by the petitioner by summing the individual fractions.

Allyl label:

Table B.7.1.1-7. Distribution of the Parent and the Metabolites in Carrot Matrices Following Application of [allyl-2-^{14}C]Clethodim at 0.557 lb ai/A (624 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =3.888 ppm)		(TRR = 0.738 ppm)		(TRR =0.752 ppm)		(TRR = 0.131 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	76.1	2.960	70.9	0.523	74.7	0.562	77.1	0.101
Clethodim	0.1	0.005	0.1	0.001	--	--	--	--
Clethodim sulfoxide (total)[1]	19.4	0.757	22.1	0.163	21.7	0.164	24.4	0.032
Clethodim sulfoxide (M29)	[7.3]	[0.285]	[7.2]	[0.053]	[9.5]	[0.072]	[7.6]	[0.010]
Clethodim sulfoxide (M37)	[12.1]	[0.472]	[14.9]	[0.110]	[12.2]	[0.092]	[16.8]	[0.022]
Clethodim sulfone (total)[1]	6.1	0.234	7.7	0.057	6.0	0.046	9.9	0.013
Clethodim sulfone (M33)	[4.0]	[0.154]	[5.0]	[0.037]	[3.4]	[0.026]	[6.1]	[0.008]
Clethodim sulfone (M41)	[2.1]	[0.080]	[2.7]	[0.020]	[2.6]	[0.020]	[3.8]	[0.005]
3-chloroallyl alcohol glucoside (M15A)	4.8	0.185	6.5	0.048	3.6	0.027	3.1	0.004
2-(Glutamyl-cysteinyl)-3-chloroacrylic acid (M22A)	7.3	0.282	--	--	7.3	0.055	--	--
Clethodim sulfoxide glucoside (M26)	9.9	0.385	--	--	14.6	0.111	--	--
Unknown M3A (polar, acidic)	3.2	0.124	11.0	0.081	0.8	0.006	15.3	0.020
Unknown M17A	--	--	0.9	0.007	--	--	6.1	0.008
Unknown M18A	0.6	0.024	--	--	--	--	--	--
Unknown M19A	4.6	0.177	--	--	4.5	0.034	--	--
Unknown M24A	1.9	0.075	--	--	5.7	0.043	--	--
Unknown M27	5.8	0.225	3.4	0.025	7.0	0.053	2.3	0.003
CAN	1.9	0.073	3.8	0.028	2.9	0.022	3.1	0.004
ACN/0.2 N HCl	2.9	0.112	3.7	0.027	2.3	0.017	2.3	0.003
ACN/0.2 N NH_4OH	2.7	0.105	3.7	0.027	1.9	0.014	1.5	0.002
0.05 M EDTA	2.1	0.081	2.8	0.021	1.5	0.011	<0.1	<0.001
1 N HCl	4.0	0.157	4.9	0.036	3.2	0.024	3.8	0.005
24% KOH	8.2	0.319	7.2	0.053	10.8	0.081	9.9	0.013
DCM (pH 14)	0.2	0.009	0.3	0.002	0.3	0.002	0.3	<<0.001
DCM (pH 2)	0.2	0.010	0.3	0.002	0.3	0.003	0.7	0.001
Aqueous	7.7	0.300	6.6	0.049	10.6	0.080	8.9	0.012
24% KOH filter paper	<0.1	0.001	0.4	0.003	0.5	0.004	0.8	0.001
Nonextractable	2.1	0.080	2.7	0.020	2.3	0.017	2.3	0.003

[1] Residues of clethodim sulfoxide and clethodim sulfone eluted in two peaks as the result of *syn/anti* inter-conversion of oxime ethers. Total values were calculated by the petitioner by summing the individual fractions.

C. Storage Stability of Residues

Samples were stored frozen (~-20 °C) from harvest to analysis. The petitioner provided the dates of harvest and HPLC analysis for all samples. Samples of immature and mature carrot tops and roots were initially analyzed within 40-42 days (1.3-1.4 months) of harvest. Based on dated chromatograms, LC/MS analyses of immature foliage extracts were completed within 228 days (7.5 months) of harvest. Although storage stability was not specifically addressed, repeat HPLC analysis of the ACN/water extracts of immature tops, ostensibly to demonstrate the stability of the metabolite profile, was conducted within 216 days (7.1 months) of harvest. Comparison of the chromatograms suggests that despite some changes, the metabolite profile was generally stable during frozen storage in terms of the relative distribution of the metabolites.

Table B.7.1.1-8. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Study Duration[1]	Interval of Demonstrated Storage Stability
Carrot roots and tops	~-20	40-42 days (1.3-1.4 months)	7.1 months

[1] Interval between harvest and HPLC analysis.

D. Identity of Residues in Carrot

The characterization and identification of radioactivity in carrot tops and roots is presented in Tables B.7.1.1-9 (ring label) and B.7.1.1-10 (allyl label).

Ring label:

Table B.7.1.1-9. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.569 lb ai/A (638 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR = 5.714 ppm)		(TRR = 0.815 ppm)		(TRR = 0.842 ppm)		(TRR = 0.158 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Clethodim	<0.1	0.004	0.2	0.002	--	--	--	--
Clethodim sulfoxide	11.8	0.663	16.2	0.132	11.3	0.095	18.4	0.029
Clethodim sulfone	3.2	0.180	6.3	0.051	4.8	0.040	7.0	0.011
Dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R)	10.5	0.594	7.7	0.063	3.6	0.030	12.0	0.019
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M17R)	9.2	0.519	13.1	0.107	8.9	0.075	13.9	0.022
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M18R)	7.3	0.410	8.8	0.072	8.1	0.068	12.7	0.020
Imine glucose conjugate (M19R)	11.2	0.633	--	--	14.1	0.119	--	--
Clethodim imine sulfoxide and hydroxy imine sulfoxide (M22R)	12.6	0.710	--	--	--	--	--	--
Clethodim imine sulfone (M24R)	6.5	0.369	--	--	7.4	0.062	--	--
Clethodim sulfoxide glucoside (M26)	6.4	0.360	--	--	9.3	0.078	--	--
Unknown M3R	0.4	0.024	2.5	0.020	0.4	0.003	3.8	0.006
Unknown M27	2.4	0.133	3.2	0.026	3.1	0.026	6.3	0.010
CAN	1.0	0.057	2.9	0.024	1.3	0.011	3.8	0.006
ACN/0.2 N HCl	1.2	0.066	1.7	0.014	2.0	0.017	1.3	0.002

Table B.7.1.1-9. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.569 lb ai/A (638 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR = 5.714 ppm)		(TRR = 0.815 ppm)		(TRR = 0.842 ppm)		(TRR = 0.158 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/0.2 N NH_4OH	1.9	0.109	2.5	0.020	1.9	0.016	--	--
0.05 M EDTA	1.5	0.085	1.5	0.012	1.3	0.011	--	--
1 N HCl	1.8	0.101	2.0	0.016	1.5	0.013	--	--
24% KOH	4.8	0.276	3.3	0.027	7.5	0.063	--	--
24% KOH filter paper	0.1	0.004	0.1	0.001	0.1	0.001	--	--
Total extractable	99.4	5.676	98.4	0.802	99.0	0.834	91.8	0.145
Total identified	<78.8	4.442	52.3	0.427	67.5	0.567	64.0	0.101
Total unidentified	15.1	0.855	19.7	0.160	19.1	0.161	15.2	0.024
Total bound residues (PES)[1]	0.7	0.038	1.6	0.013	1.0	0.008	8.2	0.013
% Accountability[2]	100		100		100		100	

[1] PES = Post-extraction solids.
[2] Total (ppm)/TRR (ppm)*100

Allyl label:

Table B.7.1.1-10. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [allyl-2-^{14}C]Clethodim at 0.557 lb ai/A (624 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =3.888 ppm)		(TRR = 0.738 ppm)		(TRR =0.752 ppm)		(TRR = 0.131 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Clethodim	0.1	0.005	0.1	0.001	--	--	--	--
Clethodim sulfoxide	19.4	0.757	22.1	0.163	21.7	0.164	24.4	0.032
Clethodim sulfone	6.1	0.234	7.7	0.057	6.0	0.046	9.9	0.013
3-chloroallyl alcohol glucoside (M15A)	4.8	0.185	6.5	0.048	3.6	0.027	3.1	0.004
2-(Glutamyl-cysteinyl)-3-chloroacrylic acid (M22A)	7.3	0.282	--	--	7.3	0.055	--	--
Clethodim sulfoxide glucoside (M26)	9.9	0.385	--	--	14.6	0.111	--	--
Unknown M3A (polar, acidic)	3.2	0.124	11.0	0.081	0.8	0.006	15.3	0.020
Unknown M17A	--	--	0.9	0.007	--	--	6.1	0.008
Unknown M18A	0.6	0.024	--	--	--	--	--	--
Unknown M19A	4.6	0.177	--	--	4.5	0.034	--	--
Unknown M24A	1.9	0.075	--	--	5.7	0.043	--	--
Unknown M27	5.8	0.225	3.4	0.025	7.0	0.053	2.3	0.003
CAN	1.9	0.073	3.8	0.028	2.9	0.022	3.1	0.004
ACN/0.2 N HCl	2.9	0.112	3.7	0.027	2.3	0.017	2.3	0.003
ACN/0.2 N NH_4OH	2.7	0.105	3.7	0.027	1.9	0.014	1.5	0.002
0.05 M EDTA	2.1	0.081	2.8	0.021	1.5	0.011	<0.1	<0.001
1 N HCl	4.0	0.157	4.9	0.036	3.2	0.024	3.8	0.005
24% KOH	8.2	0.319	7.2	0.053	10.8	0.081	9.9	0.013
24% KOH filter paper	<0.1	0.001	0.4	0.003	0.5	0.004	0.8	0.001
Total extractable	98.0	3.808	97.4	0.718	97.8	0.735	98.5	0.129
Total identified	47.6	1.848	36.4	0.269	53.2	0.403	37.4	0.049

Table B.7.1.1-10. Summary of Characterization and Identification of Radioactive Residues in Carrot Matrices Following Application of [allyl-2-^{14}C]Clethodim at 0.557 lb ai/A (624 g ai/ha).

Metabolite Fraction	Immature				Mature			
	Tops		Root		Tops		Root	
	(TRR =3.888 ppm)		(TRR = 0.738 ppm)		(TRR =0.752 ppm)		(TRR = 0.131 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Total unidentified	38.0	1.473	41.8	0.308	41.1	0.309	45.2	0.060
Total bound residues (PES)[1]	2.1	0.080	2.7	0.020	2.3	0.017	2.3	0.003
% Accountability[2]	100		100		100		101	

[1] PES = Post-extraction solids.
[2] Total (ppm)/TRR (ppm)*100

E. Proposed Metabolic Pathway

Based on the results of the carrot metabolism study, the petitioner concluded that clethodim was metabolized extensively in carrot, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring.

Figure B.7.1.1-2. Proposed Metabolic Profile of Clethodim in Carrot.

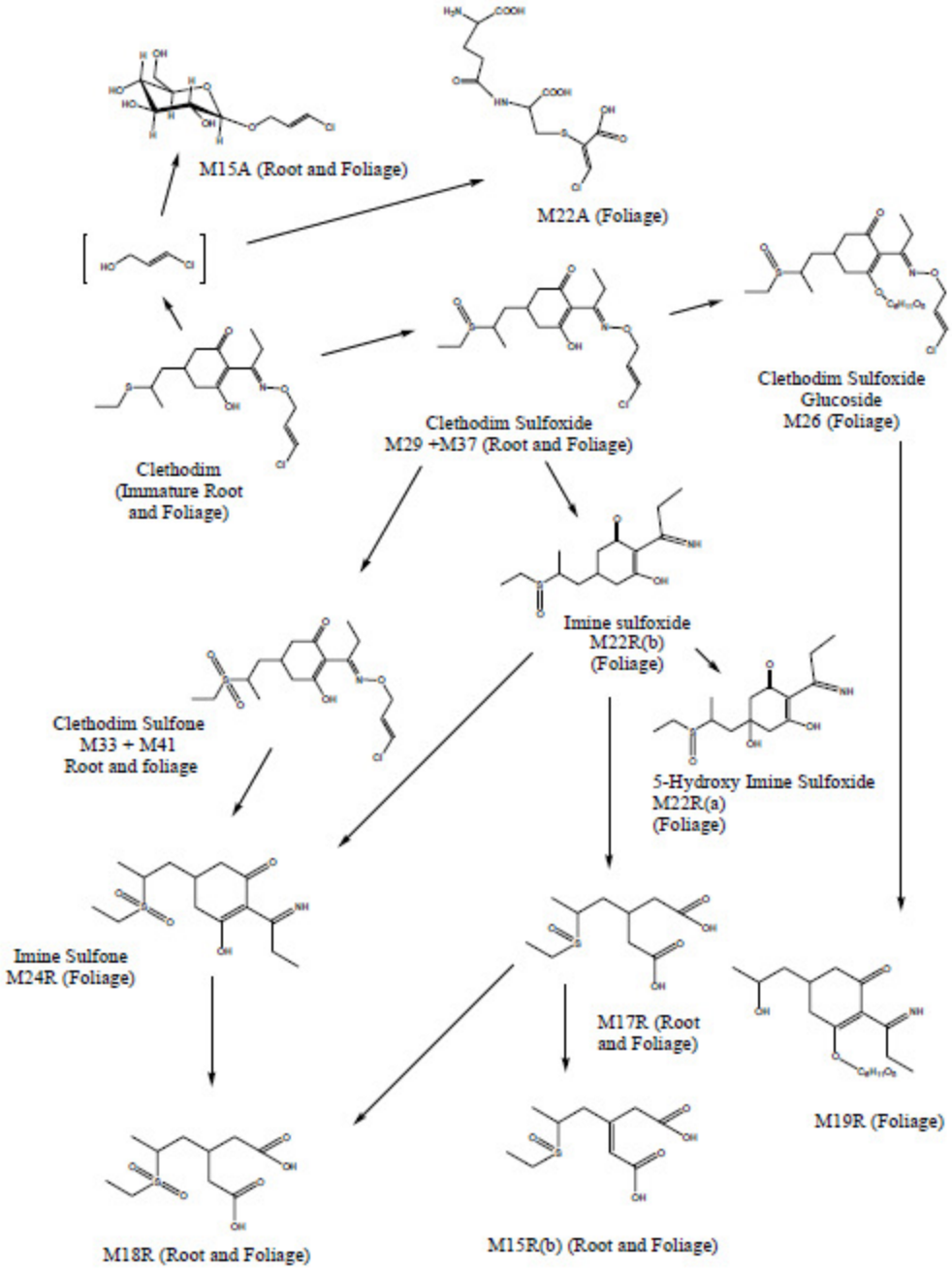


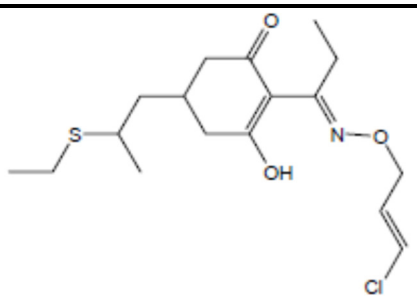
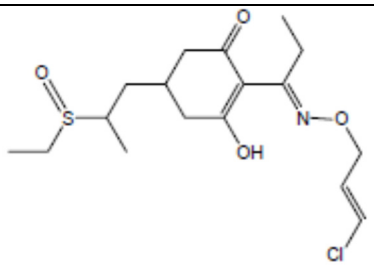
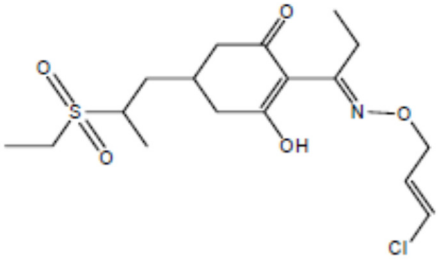
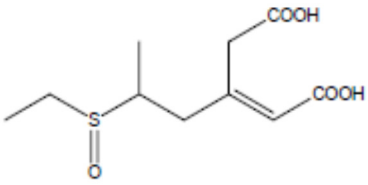
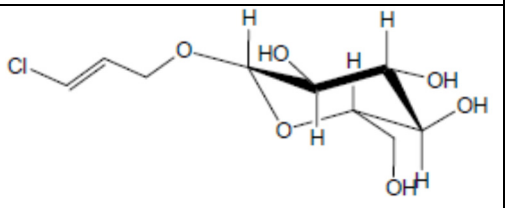
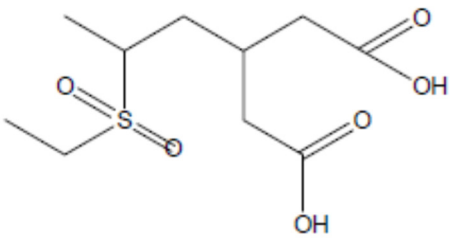
Table B.7.2.1-11. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Clethodim	(*E,E*)-(±)-2-[1[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one	
Clethodim sulfoxide; M29 and M37	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfinyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Clethodim sulfone; M33 and M41	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfonyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid; M15R (tentative identification)	Not provided	
3-Chloroallyl alcohol glucoside; M15A (tentative identification)	Not provided	
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid; M17R	Not provided	

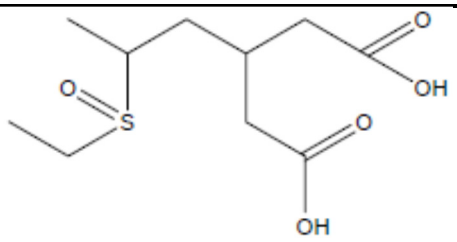
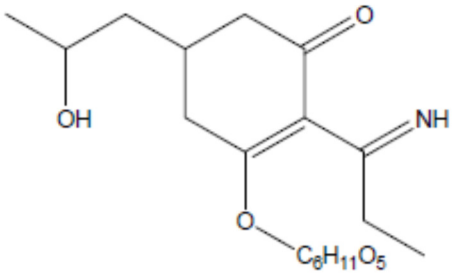
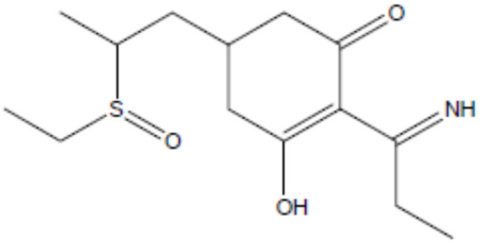
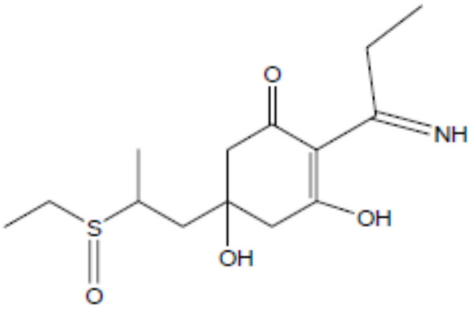
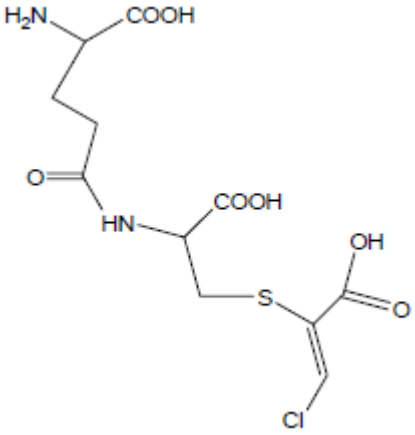
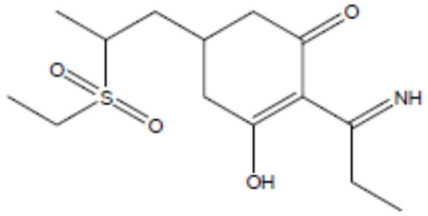
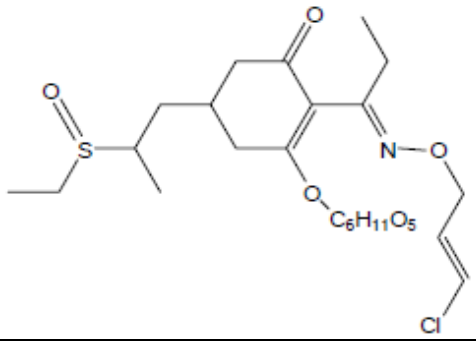
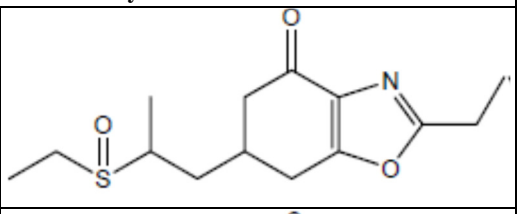
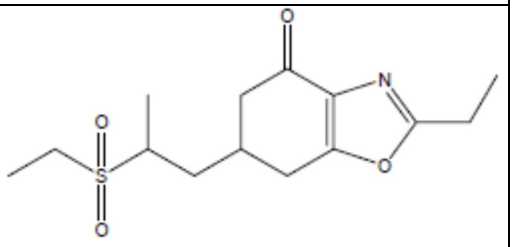
Table B.7.2.1-11. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid; M18R	Not provided	
Imine glucose conjugate; M19R (tentative identification)	Not provided	
Clethodim imine sulfoxide and hydroxy imine sulfoxide (M22R) (tentative identification)	Not provided	 and 
2-(Glutamyl-cysteinyl-3-chloroacrylic acid; M22A (tentative identification)	Not provided	

Table B.7.2.1-11. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Clethodim imine sulfone (M24R) (tentative identification)	Not provided	
Clethodim sulfoxide glucoside (M26) (tentative identification)	Not provided	
Additional reference standard compounds used in the study but not identified in any matrix		
Clethodim oxazole sulfoxide	Not provided	
Clethodim oxazole sulfone	Not provided	

III. CONCLUSIONS

The carrot metabolism study is considered scientifically acceptable. Following a single foliar broadcast application to carrots of [4,6-cyclohexen-^{14}C]clethodim (ring label) and [allyl-2-^{14}C]clethodim (allyl label) at 0.557-0.569 lb ai/A (624-638 g ai/ha), TRR, determined by summing extractable and nonextractable radioactivity were: 5.714 and 0.815 ppm in ring-label immature tops and roots and 0.842 and 0.158 ppm in ring-label mature tops and roots; 3.888 and 0.738 ppm in allyl-label immature tops and roots and 0.752 and 0.131 ppm in allyl-label mature tops and roots.

Clethodim was a minor residue component identified in the ACN/water extracts of immature tops and roots only (both labels) at <0.1-0.2% TRR. Clethodim sulfoxide was the major identified residue component in all matrices (both labels), accounting for 11.3-11.8% TRR and 16.2-18.4% TRR in ring-label tops and roots, respectively, and for 19.4-21.7% TRR and 22.1-

24.4% TRR in allyl-label tops and roots, respectively. Clethodim sulfone was also identified at slightly higher levels in roots than in tops for both labels: at 3.2-4.8% and 6.3-7.0% TRR in ring-label tops and roots, and at 6.0-6.1% and 7.7-9.9% TRR in allyl-label tops and roots. In ring-label carrots, five additional metabolites were identified or tentatively identified as major residue components in one or more matrices: (1) dehydro 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M15R) in all matrices at 3.6-10.5% TRR; (2) 3-[(2-ethylsulfinyl)propyl]-pentanedioic acid (M17R) in all matrices at 8.9-13.9% TRR; (3) 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid (M18R) in all matrices at 7.3-12.7% TRR; (4) an imine glucose conjugate (M19R) in immature and mature tops at 11.2-14.1% TRR; and (5) an imine sulfoxide and hydroxy imine sulfoxide metabolite pair (M22R) in immature tops only at 12.6% . Two additional metabolites were tentatively identified in immature and mature tops only: imine sulfone (M24R) at 6.5-7.4% TRR and clethodim sulfoxide glucoside (M26) at 6.4-9.3% TRR. Clethodim sulfoxide glucoside (M26) was the only metabolite, other than clethodim sulfoxide and sulfone that was also identified in allyl-label matrices, where it accounted for 9.9-14.6% TRR in immature and mature tops. Remaining metabolites identified in allyl-label matrices were minor components: a 3-chloroallyl glucoside (M15A) at 3.1-6.5% TRR in all matrices; and 2-(glutamyl-cysteinyl)-3-chloracrylic acid (M22A) at 7.3% TRR in immature and mature tops only. A highly polar, acidic metabolite (M3A) was a major residue component (11.0-15.3% TRR) in allyl-label roots; less radioactivity eluted with this fraction in ring-label carrot and was not investigated. No structure was proposed for M3A. Remaining discrete unknowns accounted for 2.8-10.1% TRR in ring-label carrot matrices (two unknowns) and for 12.9-17.2% TRR in allyl-label tops and 4.3-8.4% TRR in allyl-label roots.

Based on the results of the carrot metabolism study, the petitioner concluded that clethodim was metabolized extensively in carrot, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring.

REFERENCES

None

B.7.1 Metabolism, Distribution, and Expression of Residues in Plants (Annex IIA 6.2; Annex IIIA, 8.2)

B.7.1.2 Spinach

Date:	**03/05/2018**
Document ID:	MRID No. 49527102
Report:	Dohn, D., Sugiyama, K., and Woodbury, S. (2010) The Metabolism of [^{14}C]-Clethodim (2 Radiolabels) in Spinach (*Spinacea oleracea*). Laboratory Project Nos. 1809W and 1809W-1. Unpublished study prepared by Arysta LifeScience North America, LLC. 257 p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1300 Nature of the Residue - Plants, Livestock (August 1996) PMRA Regulatory Directive Dir98-02 – Residue Chemistry Guidelines, Section 2 -Nature of the Residue - Plants, Livestock OECD Guideline 501 Metabolism in Crops (January 2007)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP# 349748.
Evaluator:	William D. Wassell, Chemist RAB3/HED

Note: This Data Evaluation Record (DER) was originally prepared under contract by Versar, Inc. (6850 Versar Center, Springfield, VA 22151; submitted 7/14/15). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

Arysta Life Science EAME has submitted a study investigating the metabolism of ring-labeled [4,6-cyclohexen-^{14}C]clethodim (ring label; specific activity 1.51 MBq/mg (Megabecquerel/milligram)) and [allyl-2-^{14}C]clethodim (allyl label; specific activity 1.68 MBq/mg) following foliar application to spinach. The radiolabeled test substances were formulated as suspension concentrate (SC) formulations and applied to spinach in outdoor plots as a single foliar broadcast application at 0.481-0.508 lb ai/A (539-569 g ai/ha). Spinach was harvested at preharvest intervals (PHIs) of 14 and 28 days. The in-life phase of the study was conducted by Excel Research Services (Fresno, CA), and the analytical phase of the study was conducted by PTRL West, Inc. (Hercules CA).

Total radioactive residues (TRR) were determined by combustion/LSC (Liquid Scintillation Counting) and by summing extractable and nonextractable radioactivity. The summed TRR in spinach matrices were: 6.848 and 3.352 ppm in immature and mature ring-label spinach and 5.158 and 3.459 ppm in immature and mature allyl-label spinach.

Extraction with acetonitrile (ACN)/water released the majority of the radioactivity from immature and mature spinach matrices: 89.9-90.2% TRR for ring-label spinach and 75.3-76.7%

TRR for allyl-label spinach. Sequential extraction with ACN, ACN/0.2 N HCl (hydrochloric acid), and ACN/0.2 N NH_4OH (ammonium hydroxide) released minor amounts of radioactivity (≤2.9% TRR for any solvent in any matrix). Sequential hydrolysis of the remaining nonextractable residues with 1 N HCl and 24% KOH (potassium hydroxide) released an additional 5.3-5.9% TRR from ring-label spinach and 14.0-15.1% TRR from allyl-label spinach. Attempts to further investigate the 24% KOH hydrolysate by partitioning with DCM (dichloromethane) under acidic and basic conditions were unsuccessful. The nonextractable residues remaining following extraction and hydrolysis procedures were: 0.4-0.5% TRR (0.014-0.034 ppm) in immature and mature ring-label spinach, and 2.1% TRR (0.074-0.108 ppm) in immature and mature allyl-label spinach. These procedures adequately extracted the majority of residues from all spinach matrices. Extraction results were normalized; therefore, accountabilities were ~100%.

Residues were quantified and the clethodim sulfoxide and sulfone metabolites were identified in the ACN/water extracts of spinach by high performance liquid chromatography with ultraviolet (UV) detection (HPLC/UV). Identification of clethodim sulfoxide, clethodim sulfone, and clethodim imine sulfoxide was confirmed by thin layer co-chromatography (TLC). Remaining metabolites were identified or tentatively identified by high performance liquid chromatography with tandem mass spectrometry detection (LC/MS/MS) in conjunction with HPLC co-chromatography for certain metabolites. In addition, chromatography results were compared to those of the associated carrot metabolism study (refer to 49527101.der; B.7.1.1). Samples of immature and mature spinach were stored frozen (~-20 °C) for 35-60 days (1.2-2.0 months) prior to definitive HPLC analysis. Based on dated chromatograms, LC/MS analyses of isolated metabolites may have been completed within 314 days (10.3 months) of harvest. To demonstrate the stability of the residue profile during storage, the ACN/water extracts of all matrices were re-analyzed 256-270 days (8.4-8.9 months) after harvest. Comparison of the chromatograms suggests the metabolite profile was generally stable during frozen storage, although there were some changes in the relative amounts of certain metabolites. No additional storage stability data are required to support the study.

Clethodim was not identified in any spinach sample. Clethodim sulfoxide was identified at 2.8-3.6% TRR in ring-label spinach and at 4.7-5.1% TRR in allyl-label spinach, and clethodim sulfone was identified at 0.3-0.6% TRR in immature (both rings) and mature (allyl label) spinach. The major residue components in ring-label spinach were: (1) hydroxy 3-[(2-ethylsulfinyl)propyl]pentanedioic acid (M14R) at 12.8-14.2% TRR (0.476-0.875 ppm); (2) 3-[(2-ethylsulfinyl)propyl]pentanedioic acid (M16R/M17R) at 33.3-34.6% TRR (1.158-2.280 ppm); (3) 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid (M19R) at 9.7-12.5% TRR (0.418-0.663 ppm); and (4) an imine sulfone and hydroxy imine sulfone glucoside pair (M20R) at 9.2% TRR (0.308 ppm, mature only); (5) clethodim imine sulfoxide (M21R) at 14.3% TRR (0.979 ppm, immature only), and clethodim imine sulfone (M23R) at 6.3-7.5% TRR (0.251-0.430 ppm). Clethodim sulfoxide glucoside (M26R/M26A) was a minor residue component (≤3% TRR) in spinach from both labels. In allyl-label spinach, the major identified residue component was 3-chloroallyl glucoside (M14A/M15A) at 21.2-22.7% TRR (0.785-1.089 ppm), and the only other identified metabolite was 2-(glutamyl-cysteinyl)-3-chloropropanol (M19A) at 6.8-9.5% TRR (0.327-0.352 ppm). A highly polar, acidic metabolite (M3/4A) was a major residue component (17.5-21.0% TRR, 0.726-0.903 ppm) in allyl-label spinach. No structure was proposed for this metabolite.

Remaining discrete unknowns accounted for 6.8-7.8% TRR in ring-label matrices and 6.1-14.1% TRR in allyl-label matrices (none present at >3.9% TRR).

Based on the results of the spinach metabolism study, the petitioner concluded that clethodim was metabolized extensively in spinach, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring. The study results indicated that metabolism of clethodim in spinach was very similar to that observed in carrot.

I. MATERIALS AND METHODS

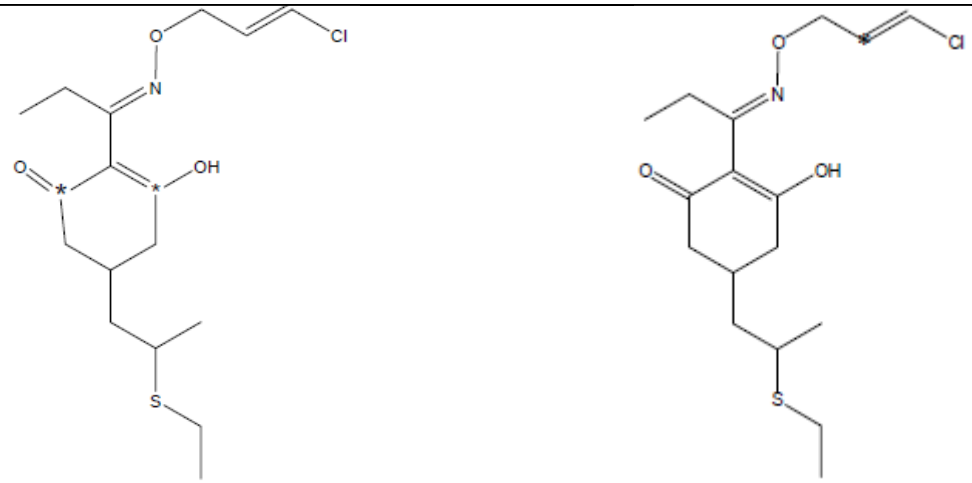
A. MATERIALS

1. Test Material

The radiolabeled test substances in ethanol were isotopically diluted with nonlabeled clethodim in ethanol. The ethanol was removed by evaporation under nitrogen, and the test substances were formulated as 2.0 lb ai/gal (240 g ai/L) SC formulations by mixing with formulation blank and water.

Table B.7.1.2-1. Clethodim Nomenclature.	
Common name	Clethodim
Identity	(*E,E*)-(±)-2-[1[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one
CAS no.	99129-21-2
Company experimental name	Not applicable
Other synonyms (if applicable)	Not applicable
Lot/Batch #	Ring label: [4,6-cyclohexen-^{14}C]clethodim: 448-151-0525
	Allyl label: [allyl-2-^{14}C]clethodim: 448-152-0597
Radiochemical purity	Ring label: 96.7%
	Allyl label: 97.7%
Specific activity as received	Ring label: 52.5 mCi/mmol (3.25 x 10^8 dpm/mg)
	Allyl label: 59.7 mCi/mmol (3.70 x 10^8 dpm/mg)
Specific activity of dose	Ring label: 1.51 MBq/mg (9.07 x 10^7 dpm/mg)
	Allyl label: 1.68 MBq/mg (1.01 x 10^8 dpm/mg)
Position of radiolabels Ring label:	Allyl label:

Table B.7.1.2-1. Clethodim Nomenclature.



2. Test Crop

The in-life phase of the study was conducted by Excel Research Services near Madera, CA, and the analytical phase of the study was conducted by PTRL West (Hercules, CA). Spinach was grown from seed in outdoor plots consisting of above-ground wooden boxes (1 m^2) filled with sandy loam soil to a depth of 15 cm. Weather conditions were reported to be normal during the experimental phase of the study. Spinach was maintained according to typical agronomic practices and was watered by hand as needed. Weather and irrigation data were provided. Plants were fertilized once; no pesticides were used during the study.

Table B.7.1.2-2. Crop Information.

Crop/Crop Group	Variety	Growth Stage at Application	Growth Stage at Harvest	Harvested Commodities
Spinach/Leafy vegetable, except brassica, group 4	Shasta	BBCH 45	Immature: BBCH 47 Mature: BBCH 49	Leaves

3. Soil Type

Table B.7.1.2-3. Soil Physicochemical Properties.

Soil Type	pH	OM %	Sand %	Silt %	Clay %	Moisture Holding Capacity (at 1/3 bar)	CEC (meg/100 g)
Sandy loam	7.5	1.4	75	16	9	11.7	9.6

OM = organic matter, CEC = cation-exchange capacity.

B. STUDY DESIGN

Experimental Conditions

The radiolabeled test substances were formulated as SC formulations and applied to spinach in outdoor plots as a single foliar broadcast application at 0.481-0.508 lb ai/A (539-569 g ai/ha) made 42 days after planting.

Table B.7.1.2-4. Use Pattern Information.

Chemical name	[4,6-cyclohexen-14C]clethodim (ring label) and [allyl-2-14C]clethodim (allyl label)
Application method	The formulated test substances were applied as a single foliar broadcast application using hand-operated pump spray nozzles
Application rate	Ring label: 0.481 lb ai/A (539 g ai/ha) Allyl label: 0.508 lb ai/A (569 g ai/ha)
Number of applications	1
Timing of applications	42 days after planting
PHI	Immature: 14 days Mature: 28 days

Sampling

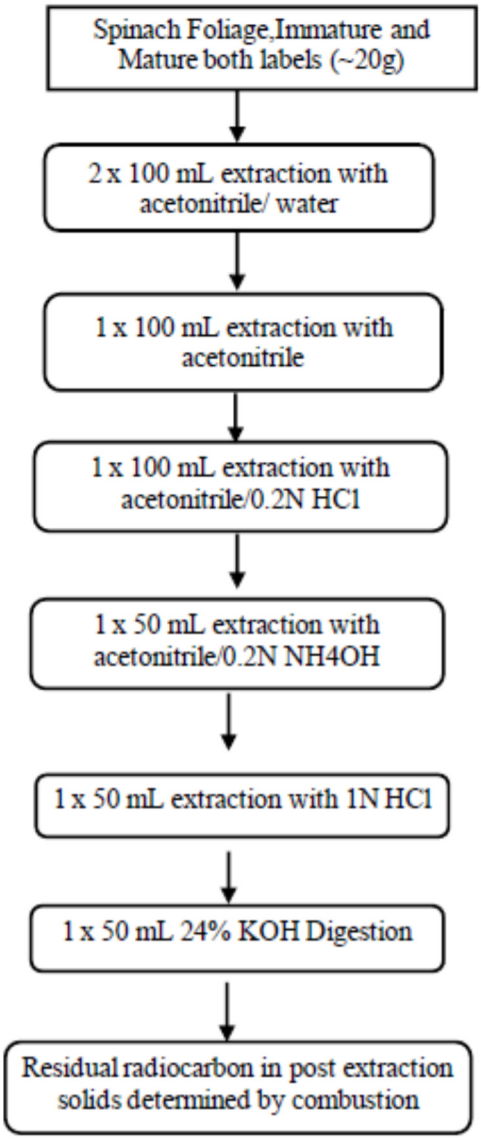
Immature and mature spinach was harvested at PHIs of 14 and 28 days, respectively. Leaves were collected by cutting ~1" above the soil line using a knife. All samples were placed in frozen storage (temperature not specified) until shipment on dry ice via FedEx to the analytical laboratory, PTRL West, Inc. (Hercules CA). At PTRL West, samples were stored frozen (~-20 °C) prior to analysis. Samples were prepared for extraction by homogenizing in the presence of dry ice.

Extraction and Analysis

Samples of spinach leaves were extracted sequentially with ACN:water (1:1, v:v; 2x), ACN, and ACN:0.2 N HCl (1:1, v:v), and were centrifuged after each step. The initial ACN/water extracts were combined, concentrated by rotary evaporation, and reserved for HPLC analysis. The nonextractable residues were subjected to further sequential extraction/hydrolysis with: (1) ACN:0.2 N NH_4OH (1:1, v:v, at ambient temperature for 45 minutes); (2) 1 N HCl (at 87 °C for 4 hours); and (3) 24% KOH (at ambient temperature, overnight). Extracts and hydrolysates were collected by centrifugation. The 24% KOH hydrolysates were vacuum filtered for further clarification, and the filter paper and its contents were reserved for combustion/LSC. The 24% KOH hydrolysates were subsequently partitioned with dichloromethane (DCM) under basic and acidic conditions (pH 14 and pH 2).

A flowchart of the extraction procedures is presented (copied without alteration from MRID 49527102) in Figure B.7.1.2-1.

FIGURE B.7.1.2-1. Extraction and Fractionation of Spinach Samples.



Identification and Characterization

The ACN/water extracts of immature and mature spinach were subjected to reverse-phase HPLC/UV (Method 2) for quantitation and identification of residues using a system equipped with a Capcell C-18 column and a UV detector (230 nm) and using a gradient mobile phase of water and ACN, each containing 0.1% formic acid. Radioactive components were detected and quantified by fraction collection coupled with LSC or using a flow-through radiodetector. In addition, metabolites were isolated and purified from the ACN/water extracts of immature and mature spinach using HPLC with fraction collection on the following systems: Method 3, using an SB-CN column and the same mobile phase with a different gradient; and Methods 4 and 5, using a Phenyl column and the same mobile phase with different gradients. Identification of clethodim sulfoxide, clethodim sulfone, and clethodim imine sulfoxide was confirmed by normal-phase TLC co-chromatography on silica gel F_{254} plates using a solvent system of chloroform:isopropanol:acetic acid (9:1:1, v:v:v). Radioactivity was detected by phosphorimaging; the nonlabeled standard was visualized under UV light. TLC was also used for analysis of purified metabolites.

The petitioner noted that clethodim and its metabolites containing the oxime ether linkage, clethodim sulfoxide and clethodim sulfone, equilibrated rapidly between their two geometric isomers (*syn* and *anti* forms) on the HPLC column; therefore, these analytes chromatographed as two distinct peaks with intervening (equilibrating molecules eluting between the two major peaks). Clethodim sulfoxide was quantitated as the sum of the two peaks and any radiocarbon eluting between the peaks; however, clethodim sulfone was quantitated on the basis of the later eluting isomer only because residues of the earlier eluting isomer were below the LOQ of the study.

To aid in identification of residues, metabolite fractions were isolated and purified from combined ACN/water extracts of ring- and allyl-label immature and mature spinach. For all matrices, the extracts were concentrated by rotary evaporation and partitioned with hexane. For immature allyl-label and mature ring-label spinach, the resulting aqueous phase was reduced under nitrogen for preparative HPLC using Method 2. Fractions were collected at 30-second intervals, and fractions corresponding to the peaks of interest were combined as appropriate. Isolated metabolites were further purified using HPLC Methods 3-5. For immature ring-label spinach, the resulting aqueous phase was fractionated by solid phase extraction on a C18 column. Residues were sequentially eluted with water, ACN/water (15%, 25%, 50%, and 75%), ACN, and 0.1% formic acid in ACN. The first four eluates, containing 95% of the radioactivity, were dried by rotary evaporation and reconstituted in the corresponding solvents for preparative HPLC using Method 2. Fractions were collected at 30-second intervals, and four fractions corresponding to the peaks of interest were combined as appropriate. Two of the isolated fractions were further purified by SPE on Supel Envi-Carb SPE cartridges. The purified metabolites from ring-label immature spinach were analyzed by TLC. All isolated metabolites were also subjected to LC/MS/MS using an LCQ Fleet mass spectrometer interfaced with HPLC. For MS/MS analysis the system used ESI in both the positive and negative scanning modes.

The following metabolites were identified in ring-label immature spinach by LC/MS/MS analysis. Metabolite M14R was tentatively identified as hydroxy 3-[(2-ethylsulfinyl)-

propyl]pentanedioic acid based on analysis of the component itself and a dehydroxylated decomposition product formed during purification. Metabolites M16R and M17R were identified in ring-label immature spinach as diastereomers of 3-[(2-ethylsulfinyl)propyl]-pentanedioic acid on the basis of LC/MS/MS and HPLC co-chromatography with a reference standard that was provided by the sponsor when the LC/MS/MS work had been completed; the reference standard also chromatographed as two distinct peaks. Metabolite M19R was identified as 3-[(2-ethylsulfonyl)propyl]pentanedioic acid on the basis of LC/MS/MS and HPLC co-chromatography. Following isolation and purification from the ACN/water extract of mature spinach, metabolite M20R was tentatively identified as a glucose conjugate of clethodim imine sulfone and/or hydroxy clethodim imine sulfone based on LC/MS/MS results characteristic for a glucose conjugate. Although not quantitated during HPLC analysis of the mature spinach extract, clethodim imine sulfoxide (M21R) was also identified following isolation from the extract of mature ring-label spinach by LC/MS/MS with confirmation by TLC co-chromatography of the 25% ACN/water eluate from SPE of immature ring-label spinach.

Metabolites M14A and M15A were tentatively identified by LC/MS/MS as alpha and beta anomers of 3-chloroallyl alcohol glucoside, and M19A was tentatively identified as 2-glutamyl-cysteinyl-3-chloropropanol on the basis of molecular weight and results characteristic of the respective conjugates. The petitioner concluded that metabolite M26 (both labels) was likely a glucose conjugate of clethodim sulfoxide on the basis of TLC co-chromatography of the metabolite isolated from immature allyl-label spinach, which indicated that a large amount of the radiolabel remained at the origin, and a small amount co-chromatographed with clethodim sulfoxide. Attempts to characterize polar Unknown M3/4A via HPLC analysis using a Luna amino column under basic conditions and LC/MS/MS analysis using a TSK gel amide column were successful only in demonstrating that the unknown consisted of one or more strongly acidic components. The petitioner concluded that the unknown corresponded to Unknown M3A in the carrot metabolism study.

The 24% KOH hydrolysates were partitioned with DCM under basic and acidic conditions in an attempt to release additional radioactivity for chromatographic analysis; however, the majority of radioactivity remained in the aqueous phase for all matrices, both labels.

II. RESULTS AND DISCUSSION

A. Total Radioactive Residues

Quantitation

TRR were determined by direct combustion/LSC and by summing extractable and nonextractable radioactivity. TRR in homogenized plant matrices and post-extraction solids (PES) were determined by combustion/LSC; TRR in surface rinses and extracts were determined by direct LSC. Summed TRR were used for all subsequent calculations.

The TRR in spinach samples are summarized in Table B.7.1.2-5.

Table B.7.1.2-5. TRR in Spinach.				
Matrix	Residues (ppm [^{14}C]clethodim equivalents)			
	Ring-label		Allyl-label	
	Combustion/LSC	Summed[1]	Combustion/LSC	Summed[1]
Immature	7.45	6.848	5.98	5.158
Mature	3.42	3.352	3.97	3.459

[1] Calculated by summing extractable and nonextractable radioactivity. These values were used for all further determinations.

B. Extraction, Characterization, and Distribution of Residues

Extraction and characterization of residues in spinach

The distribution of radioactivity in spinach is presented in Table B.7.1.2-6.

Table B.7.1.2-6. Distribution of the Parent and the Metabolites in Spinach Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.481 lb ai/A (539 g ai/ha) or [allyl-2-^{14}C]Clethodim at 0.508 lb ai/A (569 g ai/ha).

Metabolite Fraction	Ring label				Allyl label			
	Immature		Mature		Immature		Mature	
	(TRR =6.848 ppm)		(TRR = 3.352 ppm)		(TRR = 5.158 ppm)		(TRR = 3.459 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	89.9	6.156	90.2	3.023	75.3	3.882	76.7	2.654
Clethodim sulfoxide (total)[1]	2.8	0.191	3.6	0.119	5.1	0.262	4.7	0.162
Clethodim sulfoxide (M28)	[1.9]	[0.127]	[3.6]	[0.119]	[3.8]	[0.196]	[3.4]	0.119
Clethodim sulfoxide (M37)	[0.9]	[0.064]	--	--	[3.0]	[0.154]	[1.2]	[0.043]
Clethodim sulfone (M42)[1]	0.3	0.019	--	--	0.6	0.031	0.3	0.010
Hydroxy 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M14R)	12.8	0.875	14.2	0.476	--	--	--	--
3-Chloroallyl alcohol glucoside, alpha anomer (M14A)	--	--	--	--	5.7	0.292	15.1	0.521
3-Chloroallyl alcohol glucoside, beta anomer (M15A)	--	--	--	--	15.5	0.797	7.6	0.264
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid, diastereomer (M16R)	20.5	1.402	15.5	0.519	--	--	--	--
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid, diasteromer (M17R)	12.8	0.878	19.1	0.639	--	--	--	--
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M19R)	9.7	0.663	12.5	0.418	--	--	--	--
2-(Glutamyl-cysteinyl)-3-chloropropanol (M19A)	--	--	--	--	6.8	0.352	9.5	0.327
Clethodim imine sulfone and hydroxy imine sulfone glucoside (M20R)	--	--	9.2	0.308	--	--	--	--
Clethodim imine sulfoxide (M21R)	14.3	0.979	--	--	--	--	--	--
Clethodim imine sulfone (M23R)	6.3	0.430	7.5	0.251	--	--	--	--
Clethodim sulfoxide glucoside (M26R/M26A)	1.6	0.108	1.6	0.053	--	--	3.0	0.103
Unknown M3R	0.6	0.040	1.6	0.055	--	--	--	--
Unknown M3/4A	--	--	--	--	17.5	0.903	21.0	0.726
Unknowns M10R/M10A	1.3	0.089	0.5	0.017	1.9	0.098	--	--
Unknown M17A	--	--	--	--	--	--	1.9	0.066
Unknown M18A	--	--	--	--	2.2	0.114	--	--
Unknown M20A	--	--	--	--	2.2	0.112	--	--
Unknowns M25R/M25A	3.1	0.212	2.7	0.087	3.8	0.196	2.9	0.099
Unknowns M27R/M27A	1.4	0.096	1.3	0.045	3.9	0.203	--	--
Unknowns M32R/M32A	1.4	0.093	0.7	0.024	0.1	0.004	1.3	0.046
ACN	1.3	0.090	0.5	0.017	2.7	0.137	2.3	0.078
ACN/0.2 N HCl	1.7	0.119	1.2	0.040	2.9	0.151	2.8	0.096
ACN/0.2 N NH_4OH	1.3	0.086	1.8	0.061	2.0	0.101	1.8	0.061
1 N HCl	3.2	0.216	2.6	0.087	9.2	0.473	8.9	0.307
24% KOH	2.1	0.146	3.3	0.110	5.9	0.306	5.1	0.176
DCM (pH 14)	0.1	0.004	0.1	0.002	0.1	0.004	0.1	0.003
DCM (pH 2)	0.1	0.008	0.1	0.005	0.1	0.005	0.1	0.002
Aqueous	2.0	0.135	3.0	0.102	5.8	0.298	4.9	0.170
Nonextractable	0.5	0.034	0.4	0.014	2.1	0.108	2.1	0.074

[1] Residues of clethodim sulfoxide and clethodim sulfone eluted in two peaks as the result of *syn/anti* inter-conversion of oxime ethers. For clethodim sulfone only results for the major isomer were reported. Total values for clethodim sulfoxide were calculated by the petitioner by summing the individual fractions.

C. Storage Stability of Residues

Samples were stored frozen (~-20 °C) from harvest to analysis. The petitioner provided the dates of harvest and HPLC analysis for all samples. Definitive analyses for samples of immature and mature spinach were conducted within 35-60 days (1.2-2.0 months) of harvest. Based on dated chromatograms, LC/MS analyses of isolated metabolites may have been completed within 314 days (10.3 months) of harvest. To demonstrate the stability of the residue profile during storage, the ACN/water extracts of all matrices were re-analyzed 256-270 days (8.4-8.9 months) of after harvest. Comparison of the chromatograms suggests the metabolite profile was generally stable during frozen storage, although there were some changes in the relative amounts of certain metabolites.

Table B.7.1.2-7. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Study Duration[1]	Interval of Demonstrated Storage Stability
Spinach	~-20	35-60 days (1.2-2.0 months)	8.4-8.9 months

[1] Interval between harvest and definitive HPLC analysis.

D. Identity of Residues in Spinach

The characterization and identification of radioactivity in spinach is presented in Table B.7.1.2-8.

Table B.7.1.2-8. Summary of Characterization and Identification of Radioactive Residues in Spinach Matrices Following Application of [4,6-cyclohexen-^{14}C]Clethodim at 0.481 lb ai/A (539 g ai/ha) or [allyl-2-^{14}C]Clethodim at 0.508 lb ai/A (569 g ai/ha) .

Metabolite Fraction	Ring label				Allyl label			
	Immature		Mature		Immature		Mature	
	(TRR =6.848 ppm)		(TRR = 3.352 ppm)		(TRR = 5.158 ppm)		(TRR = 3.459 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Clethodim sulfoxide	2.8	0.191	3.6	0.119	5.1	0.262	4.7	0.162
Clethodim sulfone	0.3	0.019	--	--	0.6	0.031	0.3	0.010
Hydroxy 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid (M14R)	12.8	0.875	14.2	0.476	--	--	--	--
3-Chloroallyl alcohol glucoside (M14A/M15A)	--	--	--	--	21.2	1.089	22.7	0.785
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M16R/M17R)	33.3	2.280	34.6	1.158	--	--	--	--
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (M19R)	9.7	0.663	12.5	0.418	--	--	--	--
2-(Glutamyl-cysteinyl)-3-chloropropanol (M19A)	--	--	--	--	6.8	0.352	9.5	0.327
Clethodim imine sulfone and/or hydroxy imine sulfone glucoside (M20R)	--	--	9.2	0.308	--	--	--	--
Clethodim imine sulfoxide (M21R)	14.3	0.979	--	--	--	--	--	--
Clethodim imine sulfone (M23R)	6.3	0.430	7.5	0.251	--	--	--	--
Clethodim sulfoxide glucoside (M26R/M26A)	1.6	0.108	1.6	0.053	--	--	3.0	0.103
Unknown M3/4A	--	--	--	--	17.5	0.903	21.0	0.726
Minor unknowns (ea. ≤3.9% TRR)	7.8	0.530	6.8	0.228	14.1	0.727	6.1	0.211
ACN	1.3	0.090	0.5	0.017	2.7	0.137	2.3	0.078
ACN/0.2 N HCl	1.7	0.119	1.2	0.040	2.9	0.151	2.8	0.096
ACN/0.2 N NH_4OH	1.3	0.086	1.8	0.061	2.0	0.101	1.8	0.061
1 N HCl	3.2	0.216	2.6	0.087	9.2	0.473	8.9	0.307
24% KOH	2.1	0.146	3.3	0.110	5.9	0.306	5.1	0.176
Total extractable	99.5	6.813	99.6	3.338	98.0	5.050	97.6	3.372
Total identified	81.1	5.545	83.2	2.783	33.7	1.734	40.2	1.387
Total unidentified	17.4	1.187	16.2	0.543	54.3	2.798	48.0	1.655
Total bound residues (PES)[1]	0.5	0.034	0.4	0.014	2.1	0.108	2.1	0.074
% Accountability[2]	100		100		100		100	

[1] PES = Post-extraction solids.
[2] Total (ppm)/TRR (ppm)*100

E. Proposed Metabolic Pathway

Based on the results of the spinach metabolism study, the petitioner concluded that clethodim was metabolized extensively in spinach, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring.

Figure B.7.1.2-2. Proposed Metabolic Profile of Clethodim in Spinach.

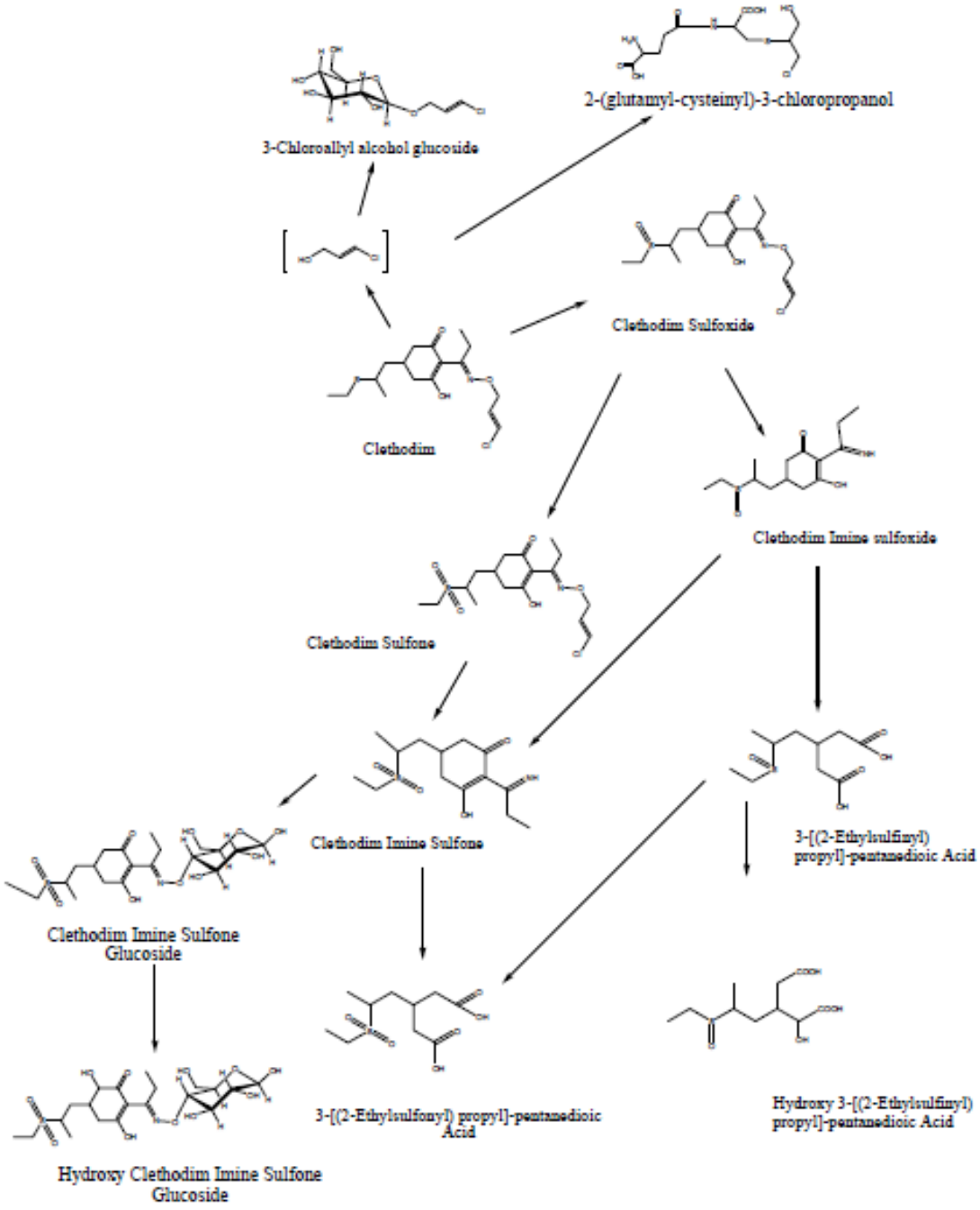


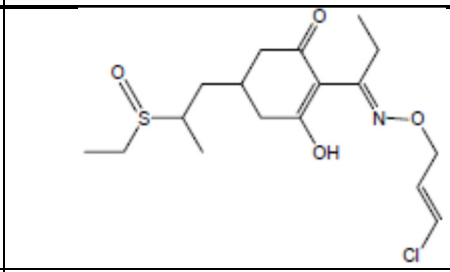
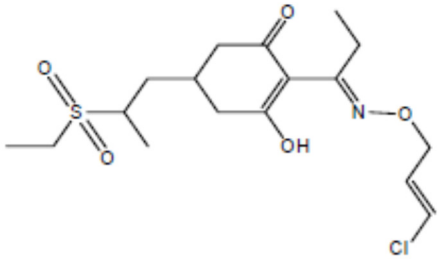
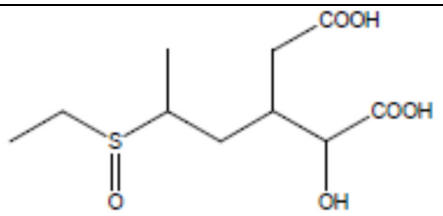
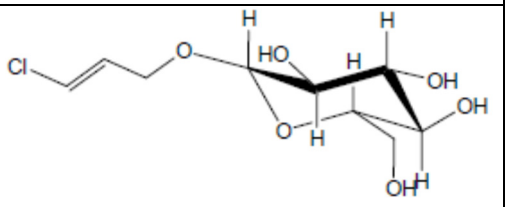
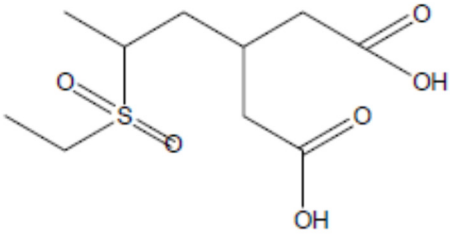
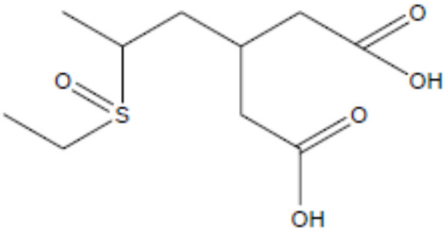
Table B.7.2.2-9. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Clethodim sulfoxide; M28 and M37	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfinyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Clethodim sulfone; M42	2-[1-[[(3-Chloro-2-propen-1-yl)oxy]imino]propyl]-5-[2-(ethylsulfonyl)propyl]-3-hydroxy-2-cyclohexen-1-one	
Hydroxy 3-[(2-ethylsulfinyl)-propyl]pentanedioic acid; M14R (tentative identification)	Not provided	
3-Chloroallyl alcohol glucoside; M14A/M15A (tentative identification)	Not provided	
3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid; M16R/M17R	Not provided	
3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid; M19R	Not provided	

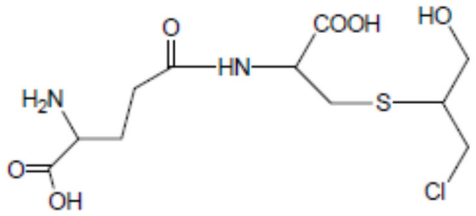
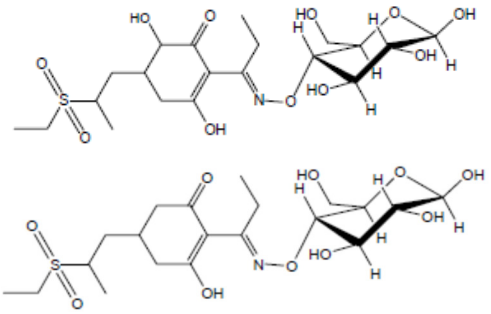
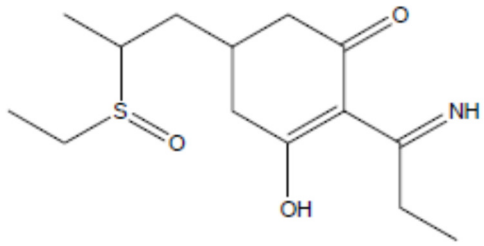
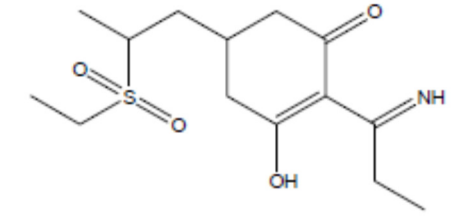
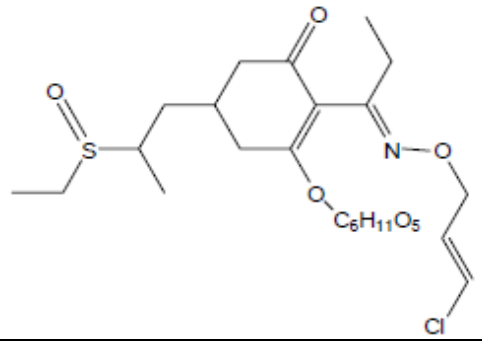
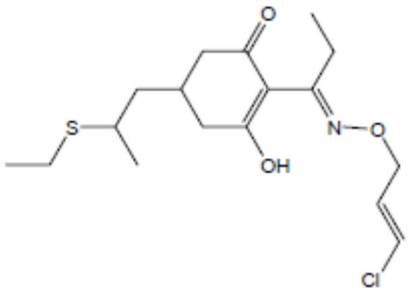
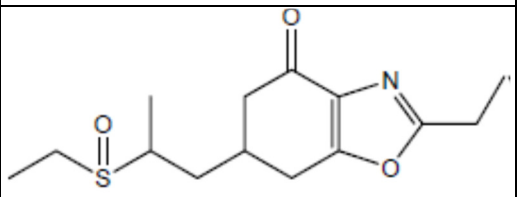
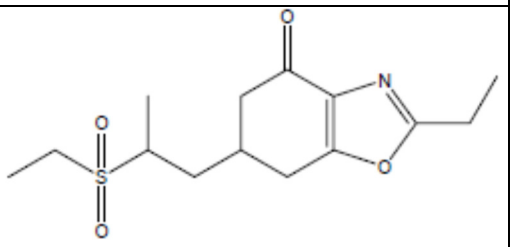
Table B.7.2.2-9. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
2-(Glutamyl-cysteinyl-3-chloropropanol; M19A (tentative identification)	Not provided	
Clethodim imine sulfone and hydroxy imine sulfone glucoside (M20R)	Not provided	
Clethodim imine sulfoxide (M21R) (tentative identification)	Not provided	
Clethodim imine sulfone (M23R) (tentative identification)	Not provided	
Clethodim sulfoxide glucoside (M26) (tentative identification)	Not provided	

Table B.7.2.2-9. Identification of Compounds from Metabolism Study (both proposed and found).		
Common Name/Code [Figure B.7.2.1 ID No.]	Chemical Name	Chemical Structure
Additional reference standard compounds used in the study but not identified in any matrix		
Clethodim	(*E,E*)-(±)-2-[1[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one	
Clethodim oxazole sulfoxide	Not provided	
Clethodim oxazole sulfone	Not provided	

III. CONCLUSIONS

The spinach metabolism study is considered scientifically acceptable. Following a single foliar broadcast application to spinach of [4,6-cyclohexen-^{14}C]clethodim (ring label) and [allyl-2-^{14}C]clethodim (allyl label) at 0.481-0.508 lb ai/A (539-569 g ai/ha), TRR, determined by summing extractable and nonextractable radioactivity were: 6.848 and 3.352 ppm in immature and mature ring-label spinach and 5.158 and 3.459 ppm in immature and mature allyl-label spinach.

Clethodim was not identified in any spinach sample. Clethodim sulfoxide was identified at 2.8-3.6% TRR in ring-label spinach and at 4.7-5.1% TRR in allyl-label spinach, and clethodim sulfone was identified at 0.3-0.6% TRR in immature (both rings) and mature (allyl label) spinach. The major residue components in ring-label spinach were: (1) hydroxy 3-[(2-ethylsulfinyl)propyl]pentanedioic acid (M14R) at 12.8-14.2% TRR; (2) 3-[(2-ethylsulfinyl)propyl]pentanedioic acid (M16R/M17R) at 33.3-34.6% TRR; (3) 3-[(2-ethylsulfonyl)propyl]-pentanedioic acid (M19R) at 9.7-12.5% TRR; and (4) an imine sulfone and hydroxy imine sulfone glucoside pair (M20R) at 9.2% TRR (mature only); (5) clethodim imine sulfoxide (M21R) at 14.3% TRR and clethodim imine sulfone (M23R) at 6.3-7.5% TRR. Clethodim sulfoxide glucoside (M26R/M26A) was a minor residue component (≤3% TRR) in spinach from both labels. In allyl-label spinach, the major identified residue component was 3-chloroallyl glucoside (M14A/M15A) at 21.2-22.7% TRR, and the only other identified metabolite was 2-(glutamyl-cysteinyl)-3-chloropropanol (M19A) at 6.8-9.5% TRR. A highly

polar, acidic metabolite (M3/4A) was a major residue component (17.5-21.0% TRR) in allyl-label spinach. No structure was proposed for this metabolite. Remaining discrete unknowns accounted for 6.8-7.8% TRR in ring-label matrices and 6.1-14.1% TRR in allyl-label matrices (none present at >3.9% TRR).

Based on the results of the spinach metabolism study, the petitioner concluded that clethodim was metabolized extensively in spinach, with the major metabolic routes being oxidation at the ethylthio group, elimination of the chloroallyl side chain, and cleavage or opening of the cyclohexanedione ring. The study results indicated that metabolism of clethodim in spinach was very similar to that observed in carrot.

REFERENCES

None

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Okra

Date:	03/05/2018
Document ID:	MRID No. 49958401
Report:	Leonard, R.C. (2015) Clethodim: Magnitude of the Residue on Okra. Report Numbers: 10383.10-YAR04; 10383. Unpublished study submitted by Interregional Research Project Number 4. 293 p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996) PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements OECD Guideline 509 Crop Field Trial (September 2009)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, D436731 & D390071.
Evaluator:	William D. Wassell, Chemist RAB3/HED

Note: This Data Evaluation Record (DER) was originally prepared under contract by CDM/CSS-Dynamac Joint Venture (3201 Jermantown Rd., Suite 400, Fairfax, VA 22030; submitted 2/28/17). The DER has been reviewed by HED and revised as necessary to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

Interregional Research Project No. 4 (IR-4) has submitted field trial data for clethodim on okra from six field trials conducted in the United States during the 2010 growing season. Trials were conducted in North American Free Trade Agreement (NAFTA) Growing Zones 2 (GA, NC, and SC; 3 trials), 3 (FL; 1 trial), 4 (AR; 1 trial), and 6 (TX; 1 trial). The above trial count reflects one pair of trials conducted at the same location that HED has determined to be replicate trials.

Each trial consisted of one untreated plot and one treated plot reflecting four broadcast foliar applications of a 0.97 lb ai/gal emulsifiable concentrate (EC) formulation of clethodim at 0.118-0.129 lb ai/A/application, with 13- to 15- day retreatment intervals, for total seasonal rates of 0.50-0.51 lb ai/A. One trial (FL) received five foliar applications for a total seasonal rate of 0.61 lb ai/A because the okra was not ready for commercial harvest following four applications. Applications were made using ground equipment in spray volumes of 20-38 gal/A. An adjuvant (nonionic surfactant) was added to the spray mixture for each application. Duplicate samples of okra were harvested at a preharvest interval (PHI) of 3 days. At one trial (NC), additional samples were collected at PHIs of 0, 8, 10, and 13 days to assess residue decline.

Samples were maintained frozen at the testing facilities, during shipping, and at the laboratory prior to analysis. The maximum storage interval for samples between harvest and extraction for analysis was 55.7 months; samples were analyzed within 29 days of extraction, except at one trial where extracts were stored refrigerated for 35 days, prior to analysis. Concurrent recovery sample extracts were also stored refrigerated for 35 days and adequate recoveries were obtained, supporting the extended extract storage period. To support sample storage durations, a concurrent storage stability study was conducted using samples of okra fortified with clethodim sulfoxide (CSO) and 5-hydroxy clethodim sulfone (5-OH CSO2) at 1.0 ppm each. The data demonstrate that residues of clethodim are stable during frozen storage in/on okra for up to 56.1 months; no 0-day data were provided. These data are acceptable to support the storage conditions and durations of samples from the submitted field trials.

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using a gas chromatography method with mass spectrometry detection (GC/MS) Method YARL-0602D, adapted from Method RM-26B-3. The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH). Residues were converted to parent equivalents by the petitioner. The limit of quantitation (LOQ; determined as the lowest level of method validation, LLMV) was 0.1 ppm for DME and DME-OH in okra, which is equivalent to 0.096 and 0.088 ppm, respectively, as clethodim equivalents. Acceptable method validation and concurrent recoveries were reported for samples of okra fortified with CSO and 5-OH CSO2 at 0.10 and 1.0 ppm, which were adequate to bracket residue levels.

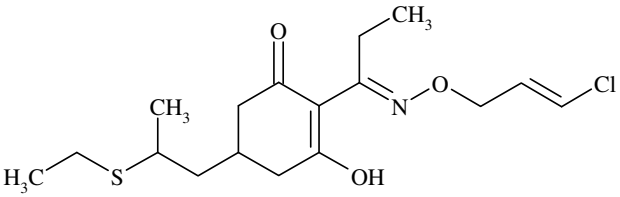
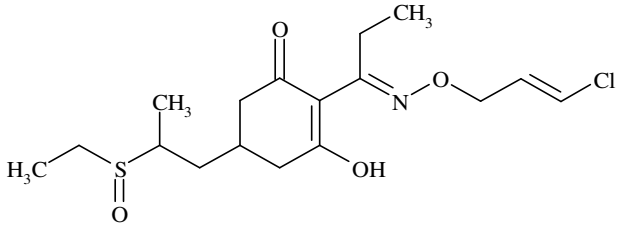
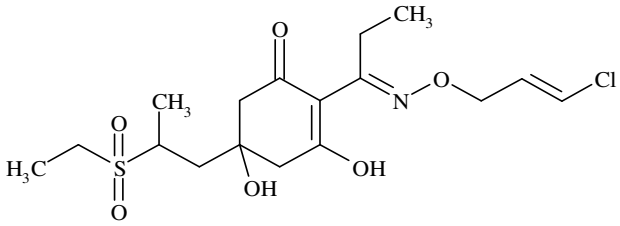
Following four broadcast foliar applications of an EC formulation of clethodim at a total seasonal rate of 0.50-0.51 lb ai/A, individual (and per-trial average) residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 ppm) and 0.115-0.478 (0.139-0.470) ppm, respectively, in/on okra harvested at a 3-day PHI; combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) were <0.211-<0.574 (<0.235-<0.566) ppm. Residues were higher in/on okra harvested at a 3-day PHI from the one trial that received five applications at a total rate of 0.61 lb ai/A: <0.096 ppm for DME and 0.429-0.582 (0.506) ppm for DME-OH, for combined residues of <0.525-<0.678 (<0.602) ppm.

In the residue decline trial, residues of DME-OH increased from the 0-day PHI to the 3-day PHI, and decreased thereafter. Residues determined as DME were below the LOQ in/on all samples from the decline trial.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for Clethodim and Metabolites of Interest.	
Common name	Clethodim
Identity	2-[1-[[[(2*E*)-3-chloro-2-propenyl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one
CAS registry number	99129-21-2
Molecular weight	359.92 g/mol
Company experimental name	Not applicable

Table B.7.6.1.1-1. Nomenclature for Clethodim and Metabolites of Interest.	
	
Metabolite	Clethodim sulfoxide (CSO)
Identity	[(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfinyl) propyl]-3-hydroxy-2-cyclohexen-1-one]
Molecular weight	375.92 g/mol
	
Metabolite	5-OH Clethodim sulfone (5-OH CSO2)
Identity	[(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfonyl) propyl]-3,5-dihydroxy-2-cyclohexen-1-one]
Molecular weight	407.92 g/mol
	

B. Study Design

1. Test Procedure

Six field trials on okra were conducted with a 0.97 lb ai/gal EC formulation of clethodim during the 2010 growing season. Field trial locations by NAFTA growing zone are summarized in Table B.7.6.1.1-2.

All trials, except for those listed in the table below, were separated by >20 miles and are therefore considered independent (568_Criteria for Independence of Trials 4/23/13 (EPA and PMRA)). The trials separated by <20 miles have been assessed for independence as detailed in the table below. HED has determined that the two trials conducted in TX should be considered a single trial with replicate samples for purposes of 860.1500 data requirements.

Independent Trial Determination[1]		
Trial Nos.	Differences	Decision
TX24, TX25	Variety: Millionaire FI (early, prolific hybrid of Clemson Spineless) vs. Clemson Spineless Timing: 22-day off-set for 1st app. *No other differences in criteria	Replicates

[1] All assessments are based on the replicate trial guidance presented in draft memo 568_Criteria for Independence of Trials 4/23/13 (EPA and PMRA).

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Okra	Sub.		3	1	1		1[2]							6
	Req.[1]		1	1	1		2							5

[1] As per Table 5 of 860.1500 for okra.
[2] Two trials conducted in Zone 6 were determined to be replicates.

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3. At the FL trial, the okra was not ready for commercial harvest after four applications, so a fifth application was made to achieve the 3-day PHI.

Table B.7.6.1.1-3. Study Use Pattern.

Location: City, State; Year (Trial ID)	End-use Product[1]	Method of Application; Timing of Application	Volume (gal/A)	Rate per Application (lb ai/A)	Retreatment Interval (days)	Total Rate (lb ai/A)	Surfactant/ Adjuvant[2]
Clinton, NC; 2010 (NC30)	0.97 lb ai/gal EC	1. Broadcast foliar; vegetative	28.1	0.122	--	0.50	NIS
		2. Broadcast foliar; vegetative	29.0	0.126	13		
		3. Broadcast foliar; flowering, some very small pods	28.8	0.126	15		
		4. Broadcast foliar; fruiting	28.4	0.124	15		
Charleston, SC; 2010 (SC*15)	0.97 lb ai/gal EC	1. Broadcast foliar; vegetative	37.6	0.126	--	0.50	NIS
		2. Broadcast foliar; bloom	37.0	0.124	15		
		3. Broadcast foliar; fruiting	37.4	0.126	13		
		4. Broadcast foliar; fruiting	37.8	0.126	14		
Tifton, GA; 2010 (GA*16)	0.97 lb ai/gal EC	1. Broadcast foliar; vegetative	32.3	0.126	--	0.51	NIS
		2. Broadcast foliar; vegetative	32.6	0.127	13		
		3. Broadcast foliar; vegetative	32.3	0.126	15		
		4. Broadcast foliar; fruiting	32.8	0.128	13		
Citra, FL; 2010 (FL41)	0.97 lb ai/gal EC	1. Broadcast foliar; vegetative	29.8, 30.1[3]	0.124	--	0.61	NIS
		2. Broadcast foliar; vegetative	29.2	0.121	13		
		3. Broadcast foliar; blooming, fruiting	30.0	0.124	15		
		4. Broadcast foliar; bloom, fruiting	28.7	0.118	14		
		5. Broadcast foliar; bloom, fruiting	30.5	0.126	14		
Alma, AR; 2010 (AR14)	0.97 lb ai/gal EC	1. Broadcast foliar; bloom, fruiting	20.5	0.127	--	0.51	NIS
		2. Broadcast foliar; fruiting	20.4	0.127	15		
		3. Broadcast foliar; bloom, fruiting	20.4	0.126	13		
		4. Broadcast foliar; fruiting	20.5	0.127	15		

Table B.7.6.1.1-3. Study Use Pattern.

Location: City, State; Year (Trial ID)	End-use Product[1]	Method of Application; Timing of Application	Volume (gal/A)	Rate per Application (lb ai/A)	Retreatment Interval (days)	Total Rate (lb ai/A)	Surfactant/ Adjuvant[2]
Weslaco, TX; 2010 (TX24)	0.97 lb ai/gal EC	1. Broadcast foliar; first true leaves	27.8	0.126	--	0.51	NIS
		2. Broadcast foliar; 3-4 true leaves	28.5	0.129	13		
		3. Broadcast foliar; flower buds present	27.7	0.125	15		
		4. Broadcast foliar; fruiting	27.6	0.125	13		
Weslaco, TX; 2010 (TX*25)	0.97 lb ai/gal EC	1. Broadcast foliar; 4-5 leaves	36.0	0.126	--	0.50	NIS
		2. Broadcast foliar; bud	35.5	0.125	14		
		3. Broadcast foliar; bloom/fruiting	35.1	0.125	13		
		4. Broadcast foliar; fruiting	35.5	0.125	14		

[1] A 0.97 lb ai/gal EC formulation of clethodim (Select® Max Herbicide) was used.
[2] NIS = Nonionic surfactant.
[3] Two tank mixes were used to treat the plot.

Okra was grown and maintained according to typical agricultural practices. Irrigation was used at all sites. Despite variations in weather conditions reported at one trial site, no unusual weather conditions were reported to have adversely affected crop production or yield during the study.

Sample Handling and Preparation

Duplicate untreated and treated samples of okra were collected 3 days after the last application at all trials except the NC trial. At the NC trial, duplicate untreated and treated samples were harvested at a 0-day PHI, and duplicate treated samples were harvested at PHIs of 3, 8, 10, and 13 days to assess residue decline. Samples were placed into frozen storage within 4 hours of harvest and were stored frozen (≤-8 °C) at the field sites prior to shipment by ACDS freezer truck or FedEx (on dry ice) to the analytical laboratory, Yakima Agricultural Research Laboratory, USDA-Agricultural Research Service (Wapato, WA). At the laboratory, samples were homogenized in the presence of dry ice and stored frozen (-23 to -1 °C) until extraction for analysis.

2. Description of Analytical Procedures

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using GC/MS Method YARL-0602D, adapted from Method RM-26B-3 entitled, "The Determination of Clethodim Residues in Crops, Chicken and Beef Tissues, Milk and Eggs" (revision dated January 20, 1994). The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH, respectively). A complete description of the method was included in the submission.

Briefly, samples were first soaked in water for 1 hour, then blended with methanol; the extract was isolated by filtration after addition of a filter aid and then concentrated, brought to volume with methanol, and diluted with water. Calcium hydroxide was added, and the extract was allowed to stand for 30 minutes before vacuum filtration and dilution with water:methanol (2:1, v:v). Following acidification with concentrated HCl and saturation with sodium chloride, the extract was partitioned (3x) with dichloromethane, and the combined organic layers were

evaporated to dryness. A 1% aqueous barium hydroxide solution was added, the mixture was heated to reflux, and the sample was oxidized using hydrogen peroxide solution. The pH was adjusted to neutral with 2 N NaOH or 2 N HCl, then excess hydrogen peroxide was removed by the addition of catalase; the mixture was acidified to pH 4.0-4.5 using potassium pyrosulfite. Glacial acetic acid was added, and the sample was evaporated to dryness. The residue was methylated using methanol and concentrated HCl at reflux, then the pH was adjusted to >7 with sodium bicarbonate solution, and the mixture was partitioned (2x) with dichloromethane. The combined organic phases were evaporated to dryness and dissolved in acetone for analysis by GC/MS. The ions monitored were: *m/z* 143, 167, and 175 for DME, and *m/z* 169, 137, and 263 for DME-OH. Residues were reported as clethodim equivalents using molecular weight conversion factors of 1.22 for DME and 1.16 for DME-OH.

The LOQ was 0.1 ppm for DME and DME-OH, based on fortification with CSO and 5-OH CSO2 at the LLMV of 0.1 ppm. The LLMV corresponds to LOQs of 0.096 and 0.088 ppm, respectively, in clethodim equivalents. The limits of detection (LODs) were calculated by multiplying the standard deviation of recovery measurements at the LLMV by the one-tailed t-statistic (99% confidence level); calculated LODs were 0.03 ppm for CSO and 0.02 ppm for 5-OH CSO2.

II. RESULTS AND DISCUSSION

Method performance was evaluated by use of method validation and concurrent recovery samples of okra fortified with combined standards of CSO and 5-OH CSO2 at 0.10-10 ppm each. Recoveries were generally within the acceptable range of 70-120%. Although low method validation recoveries (63-71%) were obtained for okra fortified with CSO at 10 ppm, concurrent recoveries of CSO were >70% at fortification levels of 0.1 and 1.0 ppm, which bracketed the observed residue levels. One concurrent recovery of CSO was high (125%; 1.0-ppm fortification level); the petitioner reported that the sample was analyzed 35 days after extraction and enough solvent may have evaporated into the headspace to increase the percent recovery. The method was considered valid for the determination of clethodim residues (CSO and 5-OH CSO2) in okra matrices (Table B.7.6.1.1-4). Concurrent recoveries were not corrected for apparent residues in controls.

The detector response was linear (coefficient of determination, $r^2 \geq 0.997$) within the range of 0.10-2.5 µg/mL. Representative chromatograms of control samples, fortified samples, and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background near the retention times of the analytes. The fortified sample chromatograms contained only the analytes of interest near the retention times of the analytes, and peaks were symmetrical and well defined. Apparent residues were nondetectable (<LOD) for DME and DME-OH in/on all control samples; we note that only one untreated sample from Trials AR14, GA*16, SC*15, and TX*25 was analyzed. The reported residue values were not corrected for apparent residues in controls.

Table B.7.6.1.1-4. Summary of Method Validation and Concurrent Recoveries of Clethodim Residues (CSO and 5-OH CSO2) from Okra.					
Matrix	Analyte	Fortification Level (ppm)	Sample Size (n)	Recoveries[1] (%)	Mean ± Std. Dev. (%)
Method Validation					
Okra	CSO (as DME)	0.10, 1.0	7	72-89	80 ± 6.3
		10	4	63, 64, 65; 71	66 ± 3.7
	5-OH CSO2 (as DME-OH)	0.10-10	11	79-98	89 ± 6.5
Concurrent Recoveries					
Okra	CSO (as DME)	0.10, 1.0	20	76-114; 125	99 ± 11
	5-OH CSO2 (as DME-OH)	0.10, 1.0	20	72-116	95 ± 10

[1] Concurrent recoveries were not corrected for apparent residues in controls.

The maximum storage interval for okra samples between harvest and extraction for analysis was 55.7 months (Table B.7.6.1.1-5a). Samples were analyzed within 29 days of extraction, except at one trial (TX24) where extracts were stored refrigerated for 35 days prior to analysis. Concurrent recovery sample extracts were also stored refrigerated for 35 days, and adequate recoveries were obtained, supporting the extended extract storage period. To support sample storage durations, a concurrent storage stability study was conducted using samples of okra fortified with CSO or 5-OH CSO2 at 1.0 ppm each. The data demonstrate that residues of clethodim are stable during frozen storage in/on okra for up to 56.1 months (Table B.7.6.1.1-5b). No 0-day data were provided; storage stability studies should always include a 0-day sampling interval to establish the residue levels present at the time samples are placed into storage [see OCSPP 860.1380(d)(6)(i)]. These data are acceptable to support the storage conditions and durations of samples from the submitted field trials.

Table B.7.6.1.1-5a. Summary of Storage Conditions.			
Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Okra	≤-1	1558-1694 days (51.2-55.7 months)	Residues of clethodim metabolites CSO and 5-OH CSO2 are stable for up to 56.1 months in/on okra.[2]

[1] Interval from harvest to extraction. Samples were analyzed within 2-35 days of extraction.
[2] Based on concurrent storage stability study; Table B.7.6.1.1-5b.

Table B.7.6.1.1-5b. Stability of Clethodim Residues in Okra Fortified with CSO and 5-OH CSO2 (≤-1 °C).							
Commodity	Analyte	Spike Level (ppm)	Storage Interval (days/months)	Fresh Fortification Recoveries (%)[1]	Stored Sample Recoveries (%)	Mean Recovery (%)	Corrected % Recovery[2]
Okra	CSO	1.0	1708/56.1	82	76, 78, 84	79	97
	5-OH CSO2	1.0	1708/56.1	81	74, 82, 87	81	100

[1] Fresh fortification recovery at 1.0 ppm. Fresh fortification was also conducted at 0.10 ppm; recoveries were 82% for CSO and 101% for 5-OH CSO2.
[2] Corrected for recovery in freshly fortified samples.

The results from the submitted field trials are presented in Tables B.7.6.1.1-6 and B.7.6.1.1-7. The trials showed that when harvested 3 days after the last of four foliar broadcast applications at a total seasonal rate of 0.50-0.51 lb ai/A, individual (and per-trial average) residues of clethodim and metabolites (determined as the sum of DME and DME-OH in clethodim equivalents) were <0.211-<0.574 (<0.235-<0.566) ppm. Clethodim residues were higher in/on okra harvested at a

3-day PHI from the one trial that received five applications at a total rate of 0.61 lb ai/A: <0.525-<0.678 (<0.602) ppm.

In the residue decline trial, residues of DME-OH increased from the 0-day PHI to the 3-day PHI, and decreased thereafter. Residues determined as DME were below the LOQ in/on all samples from the decline trial.

Table B.7.6.1.1-6. Residue Data from Okra Field Trials with Clethodim.[1]

Location: City, State; Year (Trial ID)	Zone	Okra Variety	Matrix	Rate (lb ai/A)	PHI (days)	Residues[2] (ppm clethodim equivalents) [Average]		
						DME	DME-OH	Combined[3]
Clinton, NC; 2010 (NC30)	2	Clemson Spineless	Pods	0.50	0	ND, ND [<0.095]	0.116, 0.110 [0.113]	<0.212, <0.206 [<0.209]
					3	(0.0466), (0.0489) [<0.096]	0.393, 0.405 [0.399]	<0.489, <0.501 [<0.495]
					8	(0.0367), (0.0366) [<0.096]	0.163, 0.163 [0.163]	<0.259, <0.259 [<0.259]
					10	(0.0327), ND [<0.096]	0.0982, 0.0911 [0.0947]	<0.194, <0.187 [<0.191]
					13	ND, ND [<0.096]	(0.0577), (0.0498) [<0.088]	<0.184, <0.184 [<0.184]
Charleston, SC; 2010 (SC*15)	2	Clemson Spineless	Pods	0.50	3	(0.0566), (0.0600) [<0.096]	0.478, 0.462 [0.470]	<0.574, <0.558 [<0.566]
Tifton, GA; 2010 (GA*16)	2	Clemson Spineless	Pods	0.51	3	(0.0404), (0.0358) [<0.096]	0.163, 0.115 [0.139]	<0.259, <0.211 [<0.235]
Citra, FL; 2010 (FL41)	3	Clemson Spineless 80	Pods	0.61[4]	3	(0.0637), (0.0557) [<0.096]	0.582, 0.429 [0.506]	<0.678, <0.525 [<0.602]
Alma, AR; 2010 (AR14)	4	Jefferson	Pods	0.51	3	(0.0438), ND [<0.096]	0.307, 0.273 [0.290]	<0.403, <0.369 [<0.386]
Weslaco, TX; 2010 (TX24) **and** Weslaco, TX; 2010 (TX*25)	6	Millionaire F1, Clemson Spineless	Pods	0.51, 0.50	3	(0.0366), (0.0386), ND, ND [<0.096]	0.301, 0.340, 0.276, 0.259 [0.294]	<0.397, <0.436, <0.372, <0.355 [<0.390]

[1] A 0.97 lb ai/gal EC formulation of clethodim (Select® Max Herbicide) was used.

[2] Values are the mean of duplicate analyses. The method determines residues of CSO and 5-OH CSO2 as DME and DME-OH, respectively. Residues were converted to clethodim equivalents by the petitioner using molecular weight conversion factors (1.22 for DME and 1.16 for DME-OH). ND = Not detected (<LOD). The LOQs were 0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents. The LOD was 0.03 ppm for CSO and 0.02 ppm for 5-OH CSO2. Values between the LOD and LOQ are reported in parentheses. Combined residues and per-trial averages were calculated by the study reviewer using the LOQ for all residues reported as <LOQ.

[3] Combined residues of DME and DME-OH, in clethodim equivalents.

[4] The FL site received an additional application because the okra was not ready for commercial harvest after four applications.

Table B.7.6.1.1-7. Summary of Residues from Okra Field Trials with Clethodim.

Crop Matrix	Total Application Rate (lb ai/A)	PHI (days)	Analyte	n[1]	Residues (ppm clethodim equivalents)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Okra	0.50-0.51	3	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH	5	0.115	0.478	0.139	0.470	0.294	0.318	0.126
			Combined	5	<0.211	<0.574	<0.235	<0.566	0.390	0.414	0.126
	0.61	3	DME	1	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH	1	0.429	0.582	0.506	0.506	0.506	0.506	N/A
			Combined	1	<0.525	<0.678	<0.602	<0.602	0.602	0.602	N/A

[1] n = number of field trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ are assumed to be at the LOQ (0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents). N/A = Not applicable.

III. CONCLUSIONS

The okra field trials are considered scientifically acceptable. The results of the study showed that following four broadcast foliar applications of an EC formulation of clethodim at a total seasonal rate of 0.50-0.51 lb ai/A, individual (and per-trial average) residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 ppm) and 0.115-0.478 (0.139-0.470) ppm, respectively, in/on okra harvested at a 3-day PHI; combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) were <0.211-<0.574 (<0.235-<0.566) ppm. Residues were higher in/on okra harvested at a 3-day PHI from the one trial that received five applications at a total rate of 0.61 lb ai/A: <0.096 ppm for DME, 0.429-0.582 (0.506) ppm for DME-OH, for combined residues of <0.525-<0.678 (<0.602) ppm.

In the residue decline trial, residues of DME-OH increased from the 0-day PHI to the 3-day PHI, and decreased thereafter. Residues determined as DME were below the LOQ in/on all samples from the decline trial.

An acceptable method was used for residue quantitation, and adequate storage stability data were submitted to support sample storage durations and conditions for all analytes.

REFERENCES

None.

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.2 Almond

Date:	03/05/2018
Document ID:	MRID No. 49958402
Report:	Lennon, G. (2016) Clethodim: Magnitude of the Residue on Almond. Report Numbers: 11093.13-YAR03; 11093. Unpublished study submitted by Interregional Research Project Number 4. 284 p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996) PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements OECD Guideline 509 Crop Field Trial (September 2009)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document D436731 & D190071.
Evaluator:	William D. Wassell, Chemist RAB3/HED

Note: This Data Evaluation Record (DER) was originally prepared under contract by CDM/CSS-Dynamac Joint Venture (3201 Jermantown Rd., Suite 400, Fairfax, VA 22030; submitted 2/28/17). The DER has been reviewed by HED and revised as necessary to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

Interregional Research Project No. 4 (IR-4) has submitted field trial data for clethodim on almonds from five field trials conducted in the United States during the 2013 growing season. Trials were conducted in North American Free Trade Agreement (NAFTA) Growing Zone 10 (CA).

Each trial consisted of one untreated plot and one treated plot reflecting four soil banded applications of a 0.97 lb ai/gal emulsifiable concentrate (EC) formulation of clethodim at 0.245-0.264 lb ai/A/application, with 13- to 15- day retreatment intervals, for total seasonal rates of 1.01-1.03 lb ai/A. Applications were made using ground equipment in spray volumes of 13-38 gal/A. An adjuvant (nonionic surfactant) was added to the spray mixture for each application. Duplicate samples of almond nutmeat and hulls were harvested at a preharvest interval (PHI) of 14-15 days. Residue decline was not investigated.

Samples were maintained frozen at the testing facilities, during shipping, and at the laboratory prior to analysis. The maximum storage intervals for samples from harvest to extraction for analysis were 23.6 months for almond nutmeat and 23.9 months for hulls; samples were analyzed

within 6 days of extraction. To support sample storage durations, a concurrent storage stability study was conducted using samples of almond nutmeat and hulls fortified with clethodim sulfoxide (CSO) and 5-hydroxy clethodim sulfone (5-OH CSO2) at 1.0 ppm each. The data demonstrate that residues of clethodim are stable during frozen storage in/on almond nutmeat and hulls for up to 21.8 and 22.1 months, respectively; no 0-day data were provided. These data are acceptable to support the storage conditions and durations of samples from the submitted field trials.

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using a gas chromatography method with mass spectrometry detection (GC/MS) Method YARL-0602D, adapted from Method RM-26B-3. The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH). Residues were converted to parent equivalents by the petitioner. The limit of quantitation (LOQ; determined as the lowest level of method validation, LLMV) was 0.1 ppm for DME and DME-OH in almond nutmeat and hulls, which is equivalent to 0.096 and 0.088 ppm, respectively, as clethodim equivalents. Acceptable concurrent recoveries were reported for samples of almond nutmeat and hulls fortified with CSO and 5-OH CSO2 at 0.10 and 1.0 ppm; fortification levels adequately bracketed residue levels.

Following four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 1.01-1.03 lb ai/A, residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 and <0.088 ppm, respectively) in/on almond nutmeat and hulls harvested at a 14- to 15-day PHI, for combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) of <0.184 ppm.

I. MATERIALS AND METHODS

A. MATERIALS

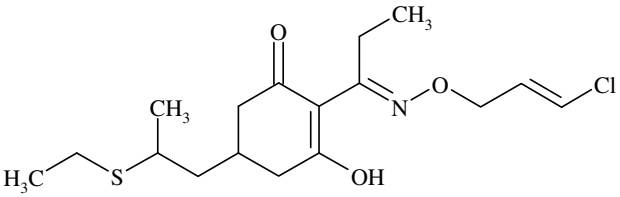
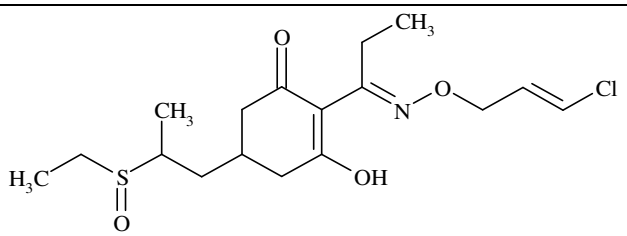
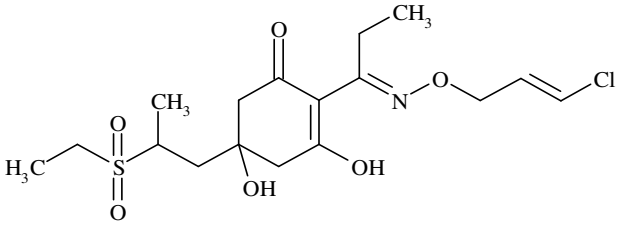
Table B.7.6.1.2-1. Nomenclature for Clethodim and Metabolites of Interest.	
Common name	Clethodim
Identity	2-[1-[[[(2*E*)-3-chloro-2-propenyl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one
CAS registry number	99129-21-2
Molecular weight	359.92 g/mol
Company experimental name	Not applicable
	
Metabolite	Clethodim sulfoxide (CSO)
Identity	[(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfinyl) propyl]-3-hydroxy-2-cyclohexen-1-one]
Molecular weight	375.92 g/mol

Table B.7.6.1.2-1. Nomenclature for Clethodim and Metabolites of Interest.	
	
Metabolite	5-OH Clethodim sulfone (5-OH CSO2)
Identity	[(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfonyl) propyl]-3,5-dihydroxy-2-cyclohexen-1-one]
Molecular weight	407.92 g/mol
	

B. Study Design

1. Test Procedure

Five field trials on almonds were conducted with a 0.97 lb ai/gal EC formulation of clethodim during the 2013 growing season. Field trial locations by NAFTA growing zone are summarized in Table B.7.6.1.2-2.

All trials, except for those listed in the table below, were separated by >20 miles and are therefore considered independent (568_Criteria for Independence of Trials 4/23/13 (EPA and PMRA)). The trials separated by <20 miles have been assessed for independence as detailed in the table below. HED has determined that there are sufficient differences between the trials that the trials may be considered separate.

Independent Trial Determination[1]		
Trial Nos.	Differences	Decision
CA115, CA116, CA117 (same site)	Variety: Padre Hard Shell for 115 vs. Non-pareil Soft Shell for 116 and 117 Timing: 21- and 27-day off-set for 1st app. for 115 vs. 116 and 117, respectively; 6-day off-set for 1st app. for 116 vs. 117. Spray volume: 13-14 GPA for 115 vs. 24-25 GPA for 116 vs. 37-38 GPA for 117 Irrigation: Microsprinkler for 115 and 116 vs. flood for 117.	CA115: Separate due to variety CA116 and CA117: Separate due to spray volume and irrigation type
CA118, CA119 (same site)	Variety: Butte Hard Shell vs. Non-pareil Soft Shell Timing: 30-day off-set for 1st app.	Separate due to variety and timing

[1] All assessments are based on the replicate trial guidance presented in draft memo 568_Criteria for Independence of Trials 4/23/13 (EPA and PMRA).

Table B.7.6.1.2-2. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Almond	Sub.										5			5
	Req.[1]										5			5

[1] As per Table 5 of 860.1500 for almond.

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.2-3. Soil banded applications were made to fine sandy loam or sandy loam soil; applications were made to the orchard floor on each side of tree row.

Table B.7.6.1.2-3. Study Use Pattern.

Location: City, State; Year (Trial ID)	End-use Product[1]	Method of Application; Timing of Application	Volume (gal/A)	Rate per Application (lb ai/A)	Retreatment Interval (days)	Total Rate (lb ai/A)	Surfactant/ Adjuvant[2]
Parlier, CA; 2013 (CA115)	0.97 lb ai/gal EC	1. Soil banded; fruiting	13	0.255	--	1.02	NIS
		2. Soil banded; fruiting	14	0.258	14		
		3. Soil banded; fruiting	13	0.254	14		
		4. Soil banded; fruiting	13	0.254	14		
Parlier, CA; 2013 (CA116)	0.97 lb ai/gal EC	1. Soil banded; fruiting	25	0.250	--	1.01	NIS
		2. Soil banded; fruiting	24	0.252	14		
		3. Soil banded; fruiting	24	0.247	14		
		4. Soil banded; fruiting	25	0.258	14		
Parlier, CA; 2013 (CA117)	0.97 lb ai/gal EC	1. Soil banded; fruiting	37	0.252	--	1.01	NIS
		2. Soil banded; fruiting	37	0.252	13		
		3. Soil banded; fruiting	38	0.254	15		
		4. Soil banded; fruiting	38	0.253	13		
Arbuckle, CA; 2013 (CA118)	0.97 lb ai/gal EC	1. Soil banded; sizing nuts/vegetative	17	0.250	--	1.02	NIS
		2. Soil banded; filling/setting nuts	18	0.258	13		
		3. Soil banded; filling nuts	17	0.245	14		
		4. Soil banded; fruiting	18	0.262	14		
Arbuckle, CA; 2013 (CA119)	0.97 lb ai/gal EC	1. Soil banded; vegetative	33	0.257	--	1.03	NIS
		2. Soil banded; vegetative/fruiting	34	0.264	13		
		3. Soil banded; vegetative/fruiting	32	0.252	15		
		4. Soil banded; fruiting/filling nuts	33	0.256	14		

[1] A 0.97 lb ai/gal EC formulation of clethodim (Select Max 1EC) was used.
[2] NIS = Nonionic surfactant.

Almonds were grown and maintained according to typical agricultural practices. Irrigation was used at all sites. No unusual weather conditions were reported to have adversely affected crop production or yield during the study.

Sample Handling and Preparation

Duplicate untreated and treated samples of almond nutmeat and hulls were collected 14-15 days after the last application. Samples were placed into frozen storage within 3.5 hours of harvest and were stored frozen (generally ≤-18 °C) at the field sites prior to shipment by ACDS freezer truck to the analytical laboratory, Yakima Agricultural Research Laboratory, USDA-Agricultural Research Service (Wapato, WA). At the laboratory, samples were homogenized in the presence of dry ice and stored frozen (-23 to -1 °C) until extraction for analysis.

2. Description of Analytical Procedures

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using GC/MS Method YARL-0602D, adapted from Method RM-26B-3 entitled, "The Determination of Clethodim Residues in Crops, Chicken and Beef Tissues, Milk and Eggs" (revision dated January 20, 1994). The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH, respectively). A complete description of the method was included in the submission.

Briefly, samples were first soaked in water for 1 hour, then blended with methanol; the extract was isolated by filtration after addition of a filter aid and then concentrated, brought to volume with methanol, and diluted with water. Calcium hydroxide was added, and the extract was allowed to stand for 30 minutes before vacuum filtration and dilution with water:methanol (2:1, v:v). Following acidification with concentrated HCl and saturation with sodium chloride, the extract was partitioned (3x) with dichloromethane, and the combined organic layers were evaporated to dryness. A 1% aqueous barium hydroxide solution was added, the mixture was heated to reflux, and the sample was oxidized using hydrogen peroxide solution. The pH was adjusted to neutral with 2 N NaOH or 2 N HCl, then excess hydrogen peroxide was removed by the addition of catalase; the mixture was acidified to pH 4.0-4.5 using potassium pyrosulfite. Glacial acetic acid was added, and the sample was evaporated to dryness. The residue was methylated using methanol and concentrated HCl at reflux, then the pH was adjusted to >7 with sodium bicarbonate solution, and the mixture was partitioned (2x) with dichloromethane. The combined organic phases were evaporated to dryness and dissolved in acetone for analysis by GC/MS. The mass ions monitored were: *m/z* 143, 167, and 175 for DME, and *m/z* 169, 137, and 263 for DME-OH. Residues were reported as clethodim equivalents using molecular weight conversion factors of 1.22 for DME and 1.16 for DME-OH.

The LOQ was 0.1 ppm for DME and DME-OH, based on fortification with CSO and 5-OH CSO2 at the LLMV of 0.1 ppm. The LLMV corresponds to LOQs of 0.096 and 0.088 ppm, respectively, in clethodim equivalents. The limit of detection was not reported.

II. RESULTS AND DISCUSSION

Method performance was evaluated by use of method validation and concurrent recovery samples of untreated almond nutmeat and hulls fortified with combined standards of CSO and 5-OH CSO2 at 0.10 and 1.0 ppm each. Recoveries were generally within the acceptable range of 70-120%. Although low method validation recoveries (61-68%) were obtained for hulls fortified with 5-OH CSO2 at 1.0 ppm, concurrent recoveries of 5-OH CSO2 from hulls were adequate at both fortification levels. The method was considered valid for the determination of clethodim residues (CSO and 5-OH CSO2) in almond matrices (Table B.7.6.1.2-4). The fortification levels bracketed the measured residues. Concurrent recoveries were not corrected for apparent residues in controls.

The detector response was linear (coefficient of determination, $r^2 \geq 0.986$) within the range of 0.025-0.30 µg/mL. Representative chromatograms of control samples, fortified samples, and treated samples were provided. The control chromatograms generally had no peaks of interest

above the chromatographic background near the retention times of the analytes. The fortified sample chromatograms contained only the analytes of interest near the retention times of the analytes, and peaks were symmetrical and well defined. Apparent residues were below the LOQ for DME and DME-OH in/on all control samples; we note that with the exception of Trials CA116 (both matrices) and CA119 (hulls), only one untreated sample of each matrix from each trial was analyzed. The reported residue values were not corrected for apparent residues in controls.

Table B.7.6.1.2-4. Summary of Method Validation and Concurrent Recoveries of Clethodim Residues (CSO and 5-OH CSO2) from Almond Matrices.

Matrix	Analyte	Fortification Level (ppm)	Sample Size (n)	Recoveries[1] (%)	Mean ± Std. Dev. (%)
Method Validation					
Almond nutmeat	CSO (as DME)	0.10, 1.0	6	83-115; 122	103 ± 14
	5-OH CSO2 (as DME-OH)	0.10, 1.0	6	97-105; 123	104 ± 9.9
Almond hulls	CSO (as DME)	0.10, 1.0	6	80-116; 122, 123	107 ± 17
	5-OH CSO2 (as DME-OH)	0.10	4	94-100	98 ± 2.7
		1.0	3	61-68	65 ± 3.6
Concurrent Recoveries					
Almond nutmeat	CSO (as DME)	0.10, 1.0	9	92-120	101 ± 11
	5-OH CSO2 (as DME-OH)	0.10, 1.0	9	91-113	103 ± 8.8
Almond hulls	CSO (as DME)	0.10, 1.0	10	77-118	95 ± 13
	5-OH CSO2 (as DME-OH)	0.10, 1.0	10	75-115	92 ± 12

[1] Concurrent recoveries were not corrected for apparent residues in controls.

The maximum storage intervals for almond samples between harvest and extraction for analysis were 23.6 months for almond nutmeat and 23.9 months for hulls (Table B.7.6.1.2-5a). Samples were analyzed within 6 days of extraction. To support sample storage durations, a concurrent storage stability study was conducted using samples of almond nutmeat and hulls fortified with CSO or 5-OH CSO2 at 1.0 ppm each. The data demonstrate that residues of clethodim are stable during frozen storage in/on almond nutmeat and hulls for up to 21.8 and 22.1 months, respectively (Table B.7.6.1.2-5b). No 0-day data were provided; storage stability studies should always include a 0-day sampling interval to establish the residue levels present at the time samples are placed into storage [see OCSPP 860.1380(d)(6)(i)]. These data are acceptable to support the storage conditions and durations of samples from the submitted field trials.

Table B.7.6.1.2-5a. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Almond nutmeat	≤-1	653-718 days (21.5-23.6 months)	Residues of clethodim metabolites CSO and 5-OH CSO2 are stable for up to 21.8 and 22.1 months in/on almond nutmeat and hulls, respectively.[2]
Almond hulls		692-726 days (22.7-23.9 months)	

[1] Interval from harvest to extraction. Samples were analyzed within 2-6 days of extraction.
[2] Based on concurrent storage stability study; Table B.7.6.1.2-5b.

Table B.7.6.1.2-5b. Stability of Clethodim Residues in Almond Fortified with CSO and 5-OH CSO2 (≤-1 °C).

Commodity	Analyte	Spike Level (ppm)	Storage Interval (days/months)	Fresh Fortification Recoveries[1] (%)	Stored Sample Recoveries (%)	Mean Recovery (%)	Corrected % Recovery[2]
Almond nutmeat	CSO	1.0	665/21.8	111	87, 91, 116	98	88
	5-OH CSO2	1.0	665/21.8	94	81, 81, 91	84	89
Almond hulls	CSO	1.0	672/22.1	105	90, 89, 113	97	92
	5-OH CSO2	1.0	672/22.1	85	72, 77, 79	76	89

[1] Fresh fortification recovery at 1.0 ppm. Fresh fortification was also conducted at 0.10 ppm; recoveries from nutmeat and hulls, respectively, were 104 and 99% for CSO, and 97 and 110% for 5-OH CSO2.
[2] Corrected for recovery in freshly fortified samples.

The results from the submitted field trials are presented in Tables B.7.6.1.2-6 and B.7.6.1.2-7. The trials showed that residues of clethodim and metabolites (determined as the sum of DME and DME-OH in clethodim equivalents) were below the LOQ (<0.184 ppm) in/on almond nutmeat and hulls harvested 14-15 days after the last of four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 1.01-1.03 lb ai/A.

Table B.7.6.1.2-6. Residue Data from Almond Field Trials with Clethodim.[1]

Location: City, State; Year (Trial ID)	Zone	Almond Variety	Rate (lb ai/A)	Matrix	PHI (days)	Residues[2] (ppm clethodim equivalents) [Average]		
						DME	DME-OH	Combined[3]
Parlier, CA; 2013 (CA115)	10	Padre Hard Shell	1.02	Nutmeat	14	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
				Hulls		<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Parlier, CA; 2013 (CA116)	10	Non-pareil Soft Shell	1.01	Nutmeat	14	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
				Hulls		<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Parlier, CA; 2013 (CA117)	10	Non-pareil Soft Shell	1.01	Nutmeat	15	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
				Hulls		<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Arbuckle, CA; 2013 (CA118)	10	Butte Hard Shell	1.02	Nutmeat	14	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
				Hulls		<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Arbuckle, CA; 2013 (CA119)	10	Non-pareil Soft Shell	1.03	Nutmeat	14	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
				Hulls		<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]

[1] A 0.97 lb ai/gal EC formulation of clethodim (Select Max 1EC) was used.
[2] Values are the mean of duplicate analyses. The method determines residues of CSO and 5-OH CSO2 as DME and DME-OH, respectively. Residues were converted to clethodim equivalents by the petitioner using molecular weight conversion factors (1.22 for DME and 1.16 for DME-OH). The LOQs were 0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents. Residues below the LOQ were not reported.
[3] Combined residues of DME and DME-OH, in clethodim equivalents.

Table B.7.6.1.2-7. Summary of Residues from Almond Field Trials with Clethodim.

Crop Matrix	Total Application Rate (lb ai/A)	PHI (days)	Analyte	n[1]	Residues (ppm clethodim equivalents)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Almond nutmeat	1.01-1.03	14-15	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH		<0.088	<0.088	<0.088	<0.088	0.088	0.088	N/A
			Combined		<0.184	<0.184	<0.184	<0.184	0.184	0.184	N/A
Almond hulls	1.01-1.03	14-15	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH		<0.088	<0.088	<0.088	<0.088	0.088	0.088	N/A
			Combined		<0.184	<0.184	<0.184	<0.184	0.184	0.184	N/A

[1] n = number of field trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ were assumed to be at the LOQ (0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents). N/A = Not applicable.

III. CONCLUSIONS

The almond field trials are considered scientifically acceptable. The results of the study showed that following four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 1.01-1.03 lb ai/A, residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 and <0.088 ppm, respectively) in/on almond nutmeat and hulls harvested at a 14- to 15-day PHI, for combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) of <0.184 ppm.

An acceptable method was used for residue quantitation, and adequate storage stability data were submitted to support sample storage durations and conditions for all analytes.

REFERENCES

None.

DATA EVALUATION RECORD

CLETHODIM

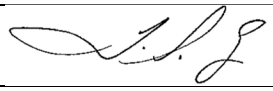
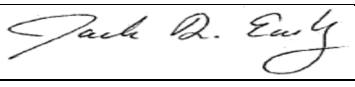
Study Type: OCSPP 860.1500, Crop Field Trial/Residue Decline

EPA Contract No. EP-W-16-018
Task Assignment Form No. 20-2-027 (MRID 49958403)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by

3201 Jermantown Rd., Suite 400
Fairfax, VA 22030

Primary Reviewer:	Signature:	
Sandra Hastings	Date:	2/17/17
Secondary Reviewer:	Signature:	
Kelly Luck, M.Sc.	Date:	2/20/17
Quality Assurance:	Signature:	
Tracy S. Lang, M.S.	Date:	2/28/17
Project Manager:	Signature:	
Jack D. Early, M.S.	Date:	2/28/17

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.3 Pecan

Date:	03/05/2018
Document ID:	MRID No. 49958403
Report:	Lennon, G. (2016) Clethodim: Magnitude of the Residue on Pecan. Report Numbers: 11094.13-YAR04; 11094. Unpublished study submitted by Interregional Research Project Number 4. 241 p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996) PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements OECD Guideline 509 Crop Field Trial (September 2009)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, D436731 & D390071.
Evaluator:	William D. Wassell, Chemist RAB3/HED

Note: This Data Evaluation Record (DER) was originally prepared under contract by CDM/CSS-Dynamac Joint Venture (3201 Jermantown Rd., Suite 400, Fairfax, VA 22030; submitted 2/28/17). The DER has been reviewed by HED and revised as necessary to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

Interregional Research Project No. 4 (IR-4) has submitted field trial data for clethodim on pecans from five field trials conducted in the United States during the 2013-2014 growing seasons. Trials were conducted in North American Free Trade Agreement (NAFTA) Growing Zones 2 (NC; 2 trials), 4 (AR; 1 trial), 6 (TX; 1 trial), and 8 (NM; 1 trial).

Each trial consisted of one untreated plot and one treated plot reflecting four soil banded applications of a 0.97 lb ai/gal emulsifiable concentrate (EC) formulation of clethodim at 0.242-0.254 lb ai/A/application, with 13- to 16- day retreatment intervals, for total seasonal rates of 0.99-1.00 lb ai/A. Applications were made using ground equipment in spray volumes of 20-38 gal/A. An adjuvant (nonionic surfactant) was added to the spray mixture for each application. Duplicate samples of pecan nutmeat were harvested at a preharvest interval (PHI) of 14-16 days; samples from two trials were stored in a cold room or a cooler on ice for 1-2 days prior to collection of nutmeats. Residue decline was not investigated.

Samples of nutmeat were maintained frozen at the testing facilities, during shipping, and at the laboratory prior to analysis. The maximum storage interval for pecan samples from harvest to

Samples of nutmeat were maintained frozen at the testing facilities, during shipping, and at the laboratory prior to analysis. The maximum storage interval for pecan samples from harvest to extraction for analysis was 19.9 months; samples were analyzed within 28 days of extraction, except at one trial where extracts were stored refrigerated for 35 days prior to analysis. Concurrent recovery sample extracts were also stored refrigerated for 35 days, and adequate recoveries were obtained, supporting the extended extract storage period. To support sample storage durations, a concurrent storage stability study was conducted using samples of pecan nutmeat fortified with clethodim sulfoxide (CSO) and 5-hydroxy clethodim sulfone (5-OH CSO2) at 1.0 ppm each. The data demonstrate that residues of clethodim are stable during frozen storage in/on pecan nutmeat for up to 19.7 months; no 0-day data were provided. These data are acceptable to support the storage conditions and durations of samples from the submitted field trials.

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using a gas chromatography method with mass spectrometry detection (GC/MS) Method YARL-0602D, adapted from Method RM-26B-3. The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH). Residues were converted to parent equivalents by the petitioner. The limit of quantitation (LOQ; determined as the lowest level of method validation, LLMV) was 0.1 ppm for DME and DME-OH in pecan, which is equivalent to 0.096 and 0.088 ppm, respectively, as clethodim equivalents. Acceptable method validation and concurrent recoveries were reported for samples of pecan nutmeat fortified with CSO and 5-OH CSO2 at 0.10 and 1.0 ppm; fortification levels adequately bracketed residue levels.

Following four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 0.99-1.00 lb ai/A, residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 and <0.088 ppm, respectively) in/on pecan nutmeat harvested at a 14- to 16-day PHI, for combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) of <0.184 ppm.

I. MATERIALS AND METHODS

A. MATERIALS

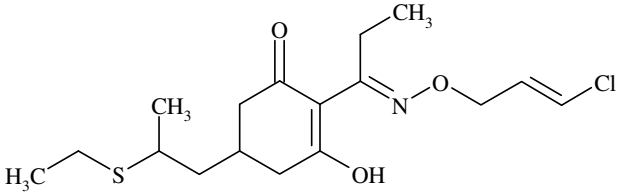
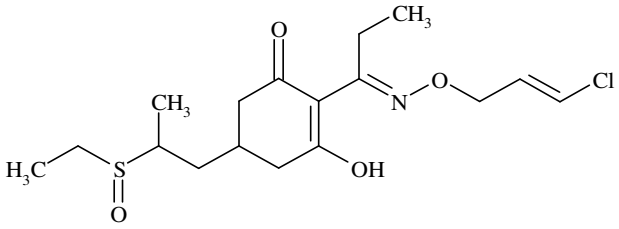
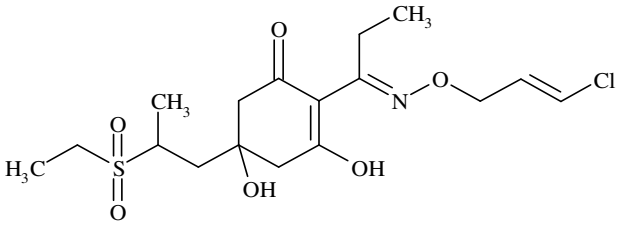
Table B.7.6.1.3-1. Nomenclature for Clethodim and Metabolites of Interest.	
Common name	Clethodim
Identity	2-[1-[[[(2*E*)-3-chloro-2-propenyl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one
CAS registry number	99129-21-2
Molecular weight	359.92 g/mol
Company experimental name	Not applicable
	

Table B.7.6.1.3-1. Nomenclature for Clethodim and Metabolites of Interest.	
Metabolite	Clethodim sulfoxide (CSO)
Identity	[(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfinyl)-propyl]-3-hydroxy-2-cyclohexen-1-one]
Molecular weight	375.92 g/mol
	
Metabolite	5-OH Clethodim sulfone (5-OH CSO2)
Identity	[(E,E)-(±)-2-[1-[[(3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylsulfonyl)-propyl]-3,5-dihydroxy-2-cyclohexen-1-one]
Molecular weight	407.92 g/mol
	

B. Study Design

1. Test Procedure

Five field trials on pecans were conducted with a 0.97 lb ai/gal EC formulation of clethodim during the 2013-2014 growing seasons. Field trial locations by NAFTA growing zone are summarized in Table B.7.6.1.3-2.

All trials, except for those listed in the table below, were separated by >20 miles and are therefore considered independent (568_Criteria for Independence of Trials 4/23/13 (EPA and PMRA)). The trials separated by <20 miles have been assessed for independence as detailed in the table below. HED has determined that there are sufficient differences between the trials that the trials may be considered separate.

Independent Trial Determination[1]		
Trial Nos.	Differences	Decision
NC19, NC284 (same site)	Variety: Stewart (both) Timing: 2013 vs 2014 growing season; 1 year off-set for 1st app.	Separate due to timing

[1] All assessments are based on the replicate trial guidance presented in draft memo 568_Criteria for Independence of Trials 4/23/13 (EPA and PMRA).

Table B.7.6.1.3-2. Trial Numbers and Geographical Locations.														
Crop	No. Trials	NAFTA Growing Zone												Total
		1	2	3	4	5	6	7	8	9	10	11	12	
Pecan	Sub.		2		1		1		1					5
	Req.[1]		2		1		1		1					5

[1] As per Table 5 of 860.1500 for pecan.

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.3-3. Soil banded applications were made to loam soils (silt loam, loamy sand, sandy loam, loam to clay loam, or sandy clay loam); applications were made to the orchard floor on each side of tree row.

Table B.7.6.1.3-3. Study Use Pattern.							
Location: City, State; Year (Trial ID)	End-use Product[1]	Method of Application; Timing of Application	Volume (gal/A)	Rate per Application (lb ai/A)	Retreatment Interval (days)	Total Rate (lb ai/A)	Surfactant/ Adjuvant[2]
Kibler, AR; 2013 (AR12)	0.97 lb ai/gal EC	1. Soil banded; fruiting	20	0.248	--	0.992	NIS
		2. Soil banded; fruiting	20	0.248	14		
		3. Soil banded; fruiting	20	0.247	14		
		4. Soil banded; fruiting	20	0.249	14		
Bailey, NC; 2013 (NC19)	0.97 lb ai/gal EC	1. Soil banded; shuck fill	38	0.249	--	0.996	NIS
		2. Soil banded; nut fill	38	0.250	14		
		3. Soil banded; nut swell	38	0.249	15		
		4. Soil banded; outer shell split	38	0.248	14		
Bailey, NC; 2014 (NC284)	0.97 lb ai/gal EC	1. Soil banded; green unopened shucks	31	0.249	--	0.994	NIS
		2. Soil banded; green unopened shucks	31	0.248	13		
		3. Soil banded; green unopened shucks	30	0.242	16		
		4. Soil banded; green shuck, early split	32	0.254	15		
Las Cruces, NM; 2013 (NM19)	0.97 lb ai/gal EC	1. Soil banded; late nut set	24	0.245	--	1.002	NIS
		2. Soil banded; nuts maturing	25	0.249	14		
		3. Soil banded; maturing nuts	25	0.253	14		
		4. Soil banded; senescing	25	0.254	15		
Falls City, TX; 2013 (TX22)	0.97 lb ai/gal EC	1. Soil banded; green pecans	25	0.250	--	0.999	NIS
		2. Soil banded; green nuts/fruiting	25	0.250	14		
		3. Soil banded; fruiting/green nuts	25	0.250	14		
		4. Soil banded; fruiting-green shells beginning to crack	25	0.250	14		

[1] A 0.97 lb ai/gal EC formulation of clethodim (Select Max 1EC) was used.
[2] NIS = Nonionic surfactant.

Pecans were grown and maintained according to typical agricultural practices. Irrigation was used only at one site (NM19). No unusual weather conditions were reported to have adversely affected crop production or yield during the study; however, in Trial AR12 heavy rains and strong winds knocked the pecans to the ground the day before harvest.

Sample Handling and Preparation

Duplicate untreated and treated samples of pecans were collected 14-16 days after the last application. The pecans were cracked open by hand or with mechanical nut crackers to harvest the nutmeat. Samples from two trials (NM19 and TX22) were stored in a cold room or a cooler on ice for 1-2 days prior to collection of nutmeats. All nutmeat samples were placed into frozen

storage within 2.5 hours of collection and were stored frozen (generally ≤-18 °C) at the field sites prior to shipment by ACDS freezer truck or FedEx (on dry ice) to the analytical laboratory, Yakima Agricultural Research Laboratory, USDA-Agricultural Research Service (Wapato, WA). At the laboratory, samples were homogenized in the presence of dry ice and stored frozen (-23 to -1 °C) until extraction for analysis.

2. Description of Analytical Procedures

Samples were analyzed for residues of clethodim and metabolites containing the 2-cyclohexen-1-one moiety using GC/MS Method YARL-0602D, adapted from Method RM-26B-3 entitled, "The Determination of Clethodim Residues in Crops, Chicken and Beef Tissues, Milk and Eggs" (revision dated January 20, 1994). The method converts residues of clethodim and metabolites to CSO and 5-OH CSO2 which are determined as their dimethyl esters (DME and DME-OH, respectively). A complete description of the method was included in the submission.

Briefly, samples were first soaked in water for 1 hour, then blended with methanol; the extract was isolated by filtration after addition of a filter aid and then concentrated, brought to volume with methanol, and diluted with water. Calcium hydroxide was added, and the extract was allowed to stand for 30 minutes before vacuum filtration and dilution with water:methanol (2:1, v:v). Following acidification with concentrated HCl and saturation with sodium chloride, the extract was partitioned (3x) with dichloromethane, and the combined organic layers were evaporated to dryness. A 1% aqueous barium hydroxide solution was added, the mixture was heated to reflux, and the sample was oxidized using hydrogen peroxide solution. The pH was adjusted to neutral with 2 N NaOH or 2 N HCl, then excess hydrogen peroxide was removed by the addition of catalase; the mixture was acidified to pH 4.0-4.5 using potassium pyrosulfite. Glacial acetic acid was added, and the sample was evaporated to dryness. The residue was methylated using methanol and concentrated HCl at reflux, then the pH was adjusted to >7 with sodium bicarbonate solution, and the mixture was partitioned (2x) with dichloromethane. The combined organic phases were evaporated to dryness and dissolved in acetone for analysis by GC/MS. The mass ions monitored were: *m/z* 143, 167, and 175 for DME, and *m/z* 169, 137, and 263 for DME-OH. Residues were reported as clethodim equivalents using molecular weight conversion factors of 1.22 for DME and 1.16 for DME-OH.

The LOQ was 0.1 ppm for DME and DME-OH, based on fortification with CSO and 5-OH CSO2 at the LLMV of 0.1 ppm. The LLMV corresponds to LOQs of 0.096 and 0.088 ppm, respectively, in clethodim equivalents. The limit of detection was not reported.

II. RESULTS AND DISCUSSION

Method performance was evaluated by use of method validation and concurrent recovery samples of untreated pecan nutmeat fortified with combined standards of CSO and 5-OH CSO2 at 0.10 and 1.0 ppm each. Recoveries were within the acceptable range of 70-120%. The method was considered valid for the determination of clethodim residues (CSO and 5-OH CSO2) in pecans (Table B.7.6.1.3-4). The fortification levels bracketed the measured residues. Concurrent recoveries were not corrected for apparent residues in controls.

The detector response was linear (coefficient of determination, $r^2 \geq 0.990$) within the range of 0.025-0.30 µg/mL. Representative chromatograms of control samples, fortified samples, and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background near the retention times of the analytes. The fortified sample chromatograms contained only the analytes of interest near the retention times of the analytes, and peaks were symmetrical and well defined. Apparent residues were below the LOQ for DME and DME-OH in/on all control samples; we note that with the exception of the Trial TX22, only one untreated sample from each trial was analyzed. The reported residue values were not corrected for apparent residues in controls.

Table B.7.6.1.3-4. Summary of Method Validation and Concurrent Recoveries of Clethodim Residues (CSO and 5-OH CSO2) from Pecan.

Matrix	Analyte	Fortification Level (ppm)	Sample Size (n)	Recoveries[1] (%)	Mean ± Std. Dev. (%)
Method Validation					
Pecan nutmeat	CSO (as DME)	0.10, 1.0	6	94-117	106 ± 9.6
	5-OH CSO2 (as DME-OH)	0.10, 1.0	6	74-100	86 ± 12
Concurrent Recoveries					
Pecan nutmeat	CSO (as DME)	0.10, 1.0	10	76-111	101 ± 11
	5-OH CSO2 (as DME-OH)	0.10, 1.0	10	70-108	92 ± 13

[1] Concurrent recoveries were not corrected for apparent residues in controls.

The maximum storage interval for pecan samples between harvest and extraction for analysis was 19.9 months (Table B.7.6.1.3-5a). Samples were analyzed within 28 days of extraction, except one sample set (TX22) that was analyzed 35 days after extraction due to problems with the calibration curve. Concurrent recovery sample extracts were also stored refrigerated for 35 days, and adequate recoveries were obtained, supporting the extended extract storage period. To support sample storage durations, a concurrent storage stability study was conducted using samples of pecan nutmeat fortified with CSO and 5-OH CSO2 at 1.0 ppm each. The data demonstrate that residues of clethodim are stable during frozen storage in/on pecan nutmeat for up to 19.7 months (Table B.7.6.1.3-5b). No 0-day data were provided; storage stability studies should always include a 0-day sampling interval to establish the residue levels present at the time samples are placed into storage [see OCSPP 860.1380(d)(6)(i)]. These data are acceptable to support the storage conditions and durations of samples from the submitted field trials.

Table B.7.6.1.3-5a. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Pecan nutmeat	≤-1	233-607 days (7.7-19.9 months)	Residues of clethodim metabolites CSO and 5-OH CSO2 are stable for up to 19.7 months in/on pecan nutmeat.[2]

[1] Interval from harvest to extraction. Samples were analyzed within 3-35 days of extraction.
[2] Based on concurrent storage stability study; Table B.7.6.1.3-5b.

Table B.7.6.1.3-5b. Stability of Clethodim Residues in Pecan Fortified with CSO and 5-OH CSO2 (≤-1 °C).							
Commodity	Analyte	Spike Level (ppm)	Storage Interval (days/months)	Fresh Fortification Recoveries[1] (%)	Stored Sample Recoveries (%)	Mean Recovery (%)	Corrected % Recovery[2]
Pecan nutmeat	CSO	1.0	599/19.7	106	117, 111, 119	116	109
	5-OH CSO2	1.0	599/19.7	108	114, 106, 115	112	103

[1] Fresh fortification recovery at 1.0 ppm. Fresh fortification was also conducted at 0.10 ppm; recoveries were 113% for CSO and 109% for 5-OH CSO2.
[2] Corrected for recovery in freshly fortified samples.

The results from the submitted field trials are presented in Tables B.7.6.1.3-6 and B.7.6.1.3-7. The trials showed that residues of clethodim and metabolites (determined as the sum of DME and DME-OH in clethodim equivalents) were below the LOQ (<0.184 ppm) in/on pecan nutmeat harvested 14-16 days after the last of four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 0.99-1.00 lb ai/A. Although the limit of detection was not reported, the peak areas for both analytes in all treated samples were reported as "0" in the raw data spreadsheets, indicating that no detectable residues of DME or DME-OH were found in/on any treated sample.

Table B.7.6.1.3-6. Residue Data from Pecan Field Trials with Clethodim.[1]								
Location: City, State; Year (Trial ID)	Zone	Pecan Variety	Rate (lb ai/A)	Matrix	PHI (days)	Residues[2] (ppm clethodim equivalents) [Average]		
						DME	DME-OH	Combined[3]
Kibler, AR; 2013 (AR12)	4	Stewart	0.992	Nutmeat	15	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Bailey, NC; 2013 (NC19)	2	Stewart	0.996	Nutmeat	16	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Bailey, NC; 2014 (NC284)	2	Stewart	0.994	Nutmeat	15	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Las Cruces, NM; 2013 (NM19)	8	Wichita/ western/ seedling	1.002	Nutmeat	14	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]
Falls City, TX; 2013 (TX22)	6	Cheyenne	0.999	Nutmeat	14	<0.096, <0.096 [<0.096]	<0.088, <0.088 [<0.088]	<0.184, <0.184 [<0.184]

[1] A 0.97 lb ai/gal EC formulation of clethodim (Select Max 1EC) was used.
[2] Values are the mean of duplicate analyses. The method determines residues of CSO and 5-OH CSO2 as DME and DME-OH, respectively. Residues were converted to clethodim equivalents by the petitioner using molecular weight conversion factors (1.22 for DME and 1.16 for DME-OH). The LOQs were 0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents. Residues below the LOQ were not reported.
[3] Combined residues of DME and DME-OH, in clethodim equivalents.

Table B.7.6.1.3-7. Summary of Residues from Pecan Field Trials with Clethodim.

Crop Matrix	Total Application Rate (lb ai/A)	PHI (days)	Analyte	n[1]	Residues (ppm clethodim equivalents)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Pecan nutmeat	0.99-1.00	14-16	DME	5	<0.096	<0.096	<0.096	<0.096	0.096	0.096	N/A
			DME-OH		<0.088	<0.088	<0.088	<0.088	0.088	0.088	N/A
			Combined		<0.184	<0.184	<0.184	<0.184	0.184	0.184	N/A

[1] n = number of field trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ were assumed to be at the LOQ (0.096 and 0.088 ppm for DME and DME-OH, respectively, in clethodim equivalents). N/A = Not applicable.

III. CONCLUSIONS

The pecan field trials are considered scientifically acceptable. The results of the study showed that following four soil banded applications of an EC formulation of clethodim at a total seasonal rate of 0.99-1.00 lb ai/A, residues of DME and DME-OH, in clethodim equivalents, were below the LOQ (<0.096 and <0.088 ppm, respectively) in/on pecan nutmeat harvested at a 14- to 16-day PHI, for combined residues of clethodim and metabolites (determined as the sum of DME and DME-OH) of <0.184 ppm in clethodim equivalents.

An acceptable method was used for residue quantitation, and adequate storage stability data were submitted to support sample storage durations and conditions for all analytes.

REFERENCES

None.